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Diabetes Mellitus Adversely Affects Sac Shrinkage and Long-Term Survival after Endovascular Aneurysm Repair

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Abstract

To explore how diabetes mellitus (DM), along with the use of metformin, shapes aneurysm sac remodeling in the aftermath of endovascular aneurysm repair (EVAR). A single-institution, retrospective cohort study was conducted among consecutive individuals who underwent elective EVAR for an infrarenal abdominal aortic aneurysm (AAA) during the period from January 2011 to December 2021. Between-group differences were assessed; Kaplan–Meier estimation was used to characterize overall survival and survival free from reintervention; and Cox regression modeling was applied to identify variables predictive of sac shrinkage. The cohort comprised 529 patients: 74 (14.0%) were living with DM and receiving metformin, 26 (4.9%) had DM but no metformin prescription, and 429 (81.1%) had no DM diagnosis. Upon evaluation at the one-year milestone, diabetic individuals exhibited a significantly lower rate of sac shrinkage relative to their non-diabetic counterparts (40.0% vs. 52.0%; P = 0.038), with a concurrent inclination toward a greater prevalence of stable sac dimensions in the diabetic subset (52% vs. 42%; P = 0.055). By the final follow-up assessment, sac shrinkage remained significantly less common among diabetics on metformin compared with non-diabetics (48.6% vs. 59.9%; P = 0.047). Comparisons between diabetic patients treated with metformin and those managed without it did not reveal any appreciable disparity in sac shrinkage. Endoleak detection rates were substantially higher within the subgroups demonstrating sac stabilization and sac enlargement. Across a surveillance period reaching nine years, overall survival was demonstrably inferior in diabetic patients compared with those free of diabetes (23.5% vs. 37.5%; P < 0.001). The evidence from this study points to a detrimental association of both diabetes mellitus and metformin therapy with aneurysm sac shrinkage following EVAR. Documentation of any endoleak category was associated with blunted sac shrinkage at both early and late observation points. Overall survival proved to be significantly compromised in the diabetic cohort compared with the non-diabetic cohort.

Keywords: Aortic aneurysm, Abdominal, Metformin, Diabetes mellitus, Endovascular aneurysm repair

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Introduction

Among patients presenting with an abdominal aortic aneurysm (AAA) who are anatomically suitable, endovascular aneurysm repair (EVAR) has emerged as the preferred strategy over conventional open surgical repair. Diminution of the aneurysm sac is widely accepted as a proxy for technically successful intervention [1] and aligns with a lower rate of adverse events extending up to 5 years post-EVAR [2]. The specific factors that dictate whether a given aneurysm will undergo shrinkage or instead remain static following EVAR are, in large part, yet to be clarified. Certain clinical and anatomical features have been implicated in blunted sac regression, including renal insufficiency, endoleaks (EL) of types I and II,

preoperative proximal neck thrombus, and aortic wall calcification [1, 3].

Diabetes mellitus (DM) stands as a firmly established contributor to cardiovascular pathology. Yet, data emerging from contemporary studies indicate that individuals afflicted with type 2 diabetes enjoy a comparatively lower likelihood of developing, experiencing enlargement of, or suffering rupture from an abdominal aortic aneurysm (AAA) [4, 5]. The biological underpinnings through which DM exerts this apparently protective influence on AAA remain incompletely characterized. However, recently published work has pointed to a thickening of the aortic wall and a retardation of matrix degradation in people with DM, effects that may be mediated by the buildup of advanced glycation end products (AGEs) and a relative scarcity of matrix metalloproteases (MMPs) [5, 6]. Such alterations are thought to contribute to the diminished risk of AAA and decelerated aneurysmal expansion.

In the pharmacological management of type 2 diabetes, metformin is the first-line therapy. Data from observational cohorts have documented lower rates of AAA enlargement among type 2 diabetic patients treated with metformin than among those receiving alternative antidiabetic regimens, a relationship that persisted even after adjustment for confounding variables [7, 8]. A recent systematic review and meta-analysis aggregated evidence and estimated a mean divergence in AAA diameter progression of approximately 0.73 mm per year between metformin users and non-users [9]. Animal model experiments have demonstrated that metformin administration curtails both the formation and the advancement of AAA [10, 11]. In earlier work from our group, we established that metformin promotes contractile function and metabolic vigor while simultaneously dampening proliferative drive, migratory capacity, and inflammatory signaling in aortic smooth muscle cells (SMCs) harvested from AAA patients and studied in vitro [12]. The conjecture that metformin may benefit AAA growth is under evaluation in randomized controlled trials (RCTs) [13-16].

In the present study, we set out to evaluate the influence of DM — both with and without metformin therapy — on the post-EVAR remodeling trajectory of the aneurysm sac, irrespective of the endograft device used. Drawing from the body of evidence outlined above, we formulated the hypothesis that both DM and metformin usage would facilitate sac stabilization and oppose sac enlargement in the post-EVAR setting. Whether these same physiological processes also modulate the degree of sac shrinkage remained an open question, which this investigation was designed to address.

Materials and Methods

Study design

This research was structured as an observational, retrospective cohort study that consecutively enrolled all patients undergoing elective EVAR for an infrarenal AAA at a single tertiary referral institution from January 2011 to December 2021. Information spanning the preoperative, intraoperative, and postoperative surveillance phases (at 6 to 8 weeks, 1 year after EVAR, and at yearly intervals thereafter) is prospectively sourced from the electronic medical record system continuously for the entire AAA patient population. It is lodged in coded format within Research Manager (Research Manager, Deventer, The Netherlands). The preoperative dataset included a foundational health evaluation performed by the anesthesiology team, which served as the basis for cataloging cardiovascular risk factors. At this same preoperative visit, the presence or absence of diabetes and the concurrent use or non-use of metformin were meticulously documented. A waiver of consent was obtained from the medical ethics committee (2023-16141), and institutional sign-off was granted by the local board of directors (2023-2183). Per institutional policy, the opt-out register was inspected to confirm that no patient had formally declined participation in scholarly research activities.

All endovascular procedures were performed in accordance with the relevant instructions for use issued by the device manufacturer and in accordance with internally established clinical protocols. Each case was reviewed in a multidisciplinary forum, and the selection of a specific endograft was guided by both anatomical parameters and the operating surgeon's discretion. Pharmacological management after the operation comprised statin agents and single-agent antiplatelet therapy, except when oral anticoagulants were clinically indicated for separate diagnoses. Upon discharge from the inpatient setting, patients typically underwent surveillance imaging within 6 to 8 weeks, including computed tomography angiography (CTA) or duplex ultrasound (DUS). Subsequent follow-up imaging — utilizing either DUS or CTA — was conducted at the first anniversary of the procedure and continued on an annual schedule thereafter. Sac diameter measurements were derived from the available imaging modality. In situations where both DUS and CTA data were available concurrently, priority was given to the CTA-derived dimensions.

Definitions

The determination of primary technical success rested on an intention-to-treat framework. To meet this benchmark, the endograft had to be introduced and deployed without incident, meaning there could be no conversion to an open procedure, no perioperative death, no type I or III endoleak, and no obstruction of any graft limb. Building upon these stipulations, should one or more unanticipated

endovascular or surgical interventions have been required to meet the intended endpoint, the case was classified under assisted technical success — marked as "yes" when the supplementary measure succeeded and "no" when it fell short.

Outcomes

The primary endpoint evaluated the effect of DM, along with metformin use, on aneurysm sac remodeling after elective EVAR. The remodeling response was stratified into three categories: sac shrinkage (a diameter contraction exceeding 5 mm from baseline), sac stability (a fluctuation of 5 mm or less in either direction relative to baseline), and sac growth (an expansion exceeding 5 mm beyond baseline). Secondary endpoints comprised the detection of EL, classified by type, alongside reintervention-free survival, all-cause survival, and freedom from aneurysm-attributable mortality, each operationalized in accordance with the reporting standards for EVAR studies [17-19].

Statistical analysis

The dataset was handled without imputing missing observations; all percentage calculations were based on the complete study arms. Conformity to a normal distribution was assessed within each group using the Shapiro–Wilk test. When distributional assumptions hold, continuous measures are summarized as the mean ± standard deviation (SD); for data that depart from normality, the median with the interquartile range (IQR) is provided instead. Categorical variables are summarized by their absolute frequencies and percentage shares. Comparative analyses across groups used independent-samples t-tests, Chi-square tests, or Mann–Whitney U tests, selected based on data type and distribution. The proportional make-up of sac remodeling status — captured at both the one-year assessment and the final available follow-up — was displayed using bar charts. The Kaplan–Meier technique was used to graph overall survival and reintervention-free survival over time, and the log-rank test was used to formally compare the resulting curves between groups. To isolate factors potentially forecasting sac shrinkage, a Cox proportional-hazards regression was constructed. All computational procedures were executed within IBM SPSS Statistics (SPSS version 29.0 for Windows, IBM Corporation, Armonk, NY, USA). Any computed two-sided P-value < 0.05 was considered statistically significant.

Results and Discussion

The original registry included 1101 individuals. From this pool, those who had undergone a planned repair of an infrarenal abdominal aortic aneurysm were deemed eligible for the present investigation. Once the prespecified elimination steps were applied, 529 individuals qualified for inclusion: 74 (14.0%) represented diabetic patients concurrently managed with metformin (DM + MF), another 26 (4.9%) comprised diabetic patients whose regimen did not include metformin (DM-MF), and the remaining 429 (81.1%) constituted the group without any diabetes diagnosis (No DM) **(Figure 1)**. The median observation window, extending to the latest recorded follow-up encounter, was 3.8 years (IQR 1.6-6.6 years), and this did not differ significantly between subgroups.

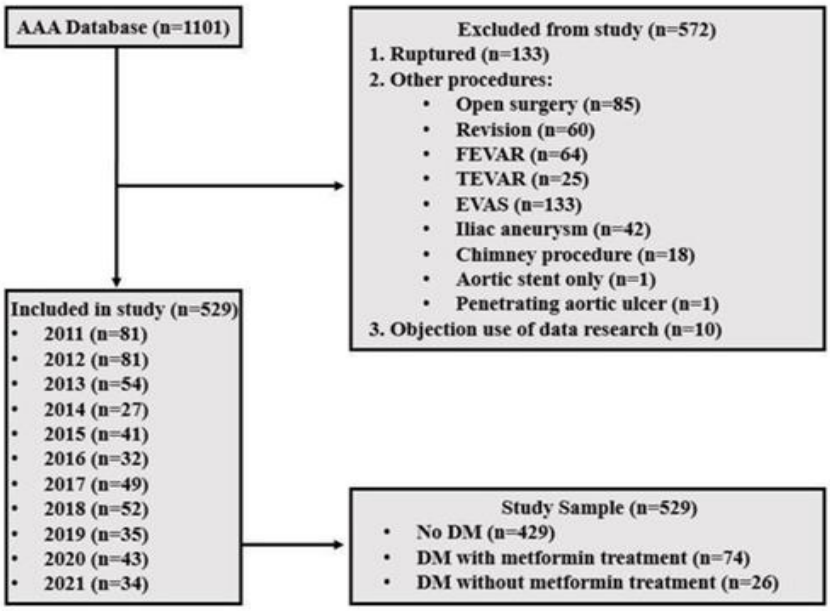


Figure 1. Flow diagram depicting patient inclusion and exclusion. Abbreviations: FEVAR = fenestrated endovascular aneurysm repair, TEVAR = thoracic endovascular aneurysm repair, EVAS = endovascular aneurysm sealing, No DM = subjects free of diabetes mellitus, and DM = diabetes mellitus.

Baseline patient and AAA characteristics

Relative to their non-diabetic counterparts, the aggregated diabetic cohort was distinguished by a greater body mass index (BMI) ($P < 0.001$), higher circulating glucose concentrations ($P < 0.001$), a shift toward worse ASA classification grades ($P < 0.001$), an elevated frequency of hypertension (HT) ($P = 0.001$) and hyperlipidemia ($P = 0.033$), and an increased prevalence of antecedent cardiac disease ($P = 0.014$) **(Table 1)**. A further observation was that diabetic patients lacking metformin therapy had a more frequent documentation of renal history ($P = 0.037$) when measured against non-diabetic individuals. Of those diabetic subjects in whom metformin was part of the pharmacologic plan, 27.0% were on metformin as a sole agent, 66.2% were concurrently receiving additional oral glucose-lowering drugs, and 37.8% were on insulin in addition to their oral diabetes medications. Turning to the diabetic subgroup for whom metformin was not part of the prescribed treatment, 38.5% were being managed with oral DM drugs, and 38.5% were receiving insulin on top of oral agents.

Table 1. Baseline characteristics per subgroup.

Baseline characteristics and aneurysm features by diabetes status							
Variable	**P-value**	**Diabetes without Metformin (n = 26)**	**P-value**	**Diabetes + Metformin (n = 74)**	**P-value**	**Diabetes overall (n = 100)**	**No diabetes (n = 429)**
Age (years)	0.164	75.2 ± 9.3	0.551	72.2 ± 7.7	0.852	73.0 ± 0.82	72.8 ± 8.1
Male (%)	0.263	24 (92.3)	0.416	65 (87.8)	0.220	89 (89.0)	361 (84.1)
BMI (kg/m²)	0.058	27.6 ± 4.5	< 0.001	27.8 (24.8–31.0)	< 0.001	27.81 (24.6–31.0)	25.8 (23.8–28.4)
Systolic BP (mmHg)	0.557	143.0 (130.0–156.0)	0.761	143.0 (125.0–160.0)	0.596	143.06 (127.5–160.0)	143.0 (127–156.5)
Diastolic BP (mmHg)	0.599	82.0 (70.0–87.0)	0.410	81.0 (74.0–87.0)	0.348	81.06 (73.0–87.0)	81.0 (74–89)
Heart Rate (bpm)	0.134	78.0 (70.0–85.0)	0.471	73.0 (66.0–85.0)	0.188	74 (66.0–85.0)	72.5 (64–84.5)
ASA ≤ 2	0.002	4 (15.4)	0.025	22 (29.7)	< 0.001	26 (26.0)	195 (46.9)
ASA ≥ 3	—	22 (84.6)	—	51 (68.9)	—	73 (73.0)	221 (53.1)
Hypertension (%)	0.012	24 (92.3)	0.011	62 (83.8)	< 0.001	86 (86.0)	293 (69.3)
Hyperlipidemia (%)	0.105	21 (80.8)	0.011	59 (79.7)	0.033	80 (87.0)	295 (76.8)
Cardiac disease history	0.324	13 (50.0)	0.017	43 (58.1)	0.014	56 (60.2)	176 (46.0)
Pulmonary disease history	0.602	4 (15.4)	0.115	20 (27.0)	0.279	24 (26.4)	79 (21.1)
Renal disease history	0.037	11 (42.3)	0.321	23 (31.1)	0.073	34 (35.4)	110 (26.3)
Smoking history	0.917	9 (34.6)	0.680	27 (36.5)	0.692	36 (37.1)	142 (35.0)
Type 2 DM (diet/oral)	—	17 (65.4)	—	60 (81.1)	—	77 (77.0)	—
Type 2 DM (insulin-treated)	—	7 (26.9)	—	14 (18.9)	—	21 (21.0)	—
Type 1 DM	—	2 (7.7)	—	—	—	2 (2.0)	—
Glucose (mmol/L)	< 0.001	8.8 (6.7–10.4)	< 0.001	9.2 (6.5–11.4)	< 0.001	9.1 (6.5–11.0)	5.7 (5.2–6.3)

Metformin use	—	—	< 0.001	74 (100)	< 0.001	74 (76.0)	—
Other oral antidiabetics	< 0.001	10 (38.5)	< 0.001	49 (66.2)	< 0.001	60 (66.7)	—
Insulin therapy	< 0.001	10 (38.5)	< 0.001	28 (37.8)	< 0.001	38 (42.2)	—
Metformin monotherapy	—	—	< 0.001	20 (27.0)	< 0.001	20 (22.2)	—

Abdominal Aortic Aneurysm (AAA) Characteristics

Variable	P-value	DM without Metformin	P-value	DM + Metformin	P-value	Diabetes overall	No diabetes
Max aneurysm diameter (mm)	0.350	55.0 (53.0–59.0)	0.794	57.0 (54.0–63.0)	0.823	56.5 (53.2–62.7)	57.0 (53.0–63.0)
Infrarenal neck diameter (mm)	0.004	26.0 (24.0–28.0)	0.696	23.0 (21.0–25.0)	0.320	24.0 (22.0–26.0)	23.5 (21.0–25.0)
Infrarenal neck length (mm)	0.610	29.0 (16.0–50.5)	0.232	30.0 (21.0–38.0)	0.212	29.5 (20.0–40.0)	27.5 (19.0–37.0)
AAA–neck angle (°)	0.327	40.0 (26.0–40.0)	0.080	30.0 (23.0–49.0)	0.052	35.0 (23.0–44.5)	41.5 (27.0–60.0)
Right CIA diameter (mm)	0.050	14.0 (11.0–18.0)	0.227	17.0 (14.0–22.5)	0.986	16.0 (13.0–19.5)	16.0 (13.0–20.0)
Left CIA diameter (mm)	0.064	13.05 (12.0–15.0)	0.099	16.0 (14.0–21.0)	0.679	15.0 (13.0–18.0)	15.0 (13.0–19.0)

Aneurysm morphology and device type

Category	P-value	DM without Metformin	P-value	DM + Metformin	P-value	Diabetes overall	No diabetes
Aneurysm type	0.831	—	0.618	—	0.749	—	—
Saccular	—	2 (7.7)	—	8 (10.8)	—	10 (10.8)	39 (9.7)
Fusiform	—	22 (84.6)	—	61 (82.4)	—	83 (89.2)	365 (90.3)
Endograft device	0.868	—	0.338	—	0.463	—	—
Medtronic endurant	—	15 (57.7)	—	40 (54.1)	—	55 (55.0)	241 (56.3)
Gore excluder	—	6 (23.1)	—	26 (35.1)	—	32 (32.0)	134 (31.3)
Endologix AFX	—	4 (15.4)	—	—	—	4 (4.0)	21 (4.9)
Other devices	—	1 (3.8)	—	8 (10.8)	—	9 (9.0)	32 (7.5)

Abbreviations: No DM = non-diabetic subjects, DM-total = the aggregate of diabetic subjects, DM + MF = diabetic subjects prescribed metformin, DM-MF = diabetic subjects whose regimen does not include metformin, BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; ASA = American Society of Anesthesiologists; DM = diabetes mellitus; AAA = abdominal aortic aneurysm, CIA = common iliac artery, P = P-value for the comparison against the non-diabetic group. Figures are expressed as mean ± SD, count (percentage), or median (Q1; Q3). [a]: Ongoing tobacco consumption encompasses those who quit less than one year prior; [b]: Type 2 diabetic individuals relying solely on insulin to manage circulating glucose; [c]: Glucose or fasting glucose concentration obtained at baseline; [d]: Covers sulfonylurea-based agents: Gliclazide, Glimepiride, and Tolbutamide; [e]: Covers the insulin products: glargine, isophane, detemir, aspart/protamine/novorapid, glulisine, and lispro.

When the diabetic and non-diabetic AAA cohorts were contrasted, no statistically appreciable discrepancy was detectable in the preoperative maximal aneurysm sac dimension, the anatomical pattern of the aneurysm, or the selected endograft platform, as documented in **Table 1**. The diabetic subset not exposed to metformin did, however, diverge from the non-diabetic group on two anatomical metrics: a broader infrarenal neck diameter was recorded (26.0 mm, IQR 24.0–28.0 mm vs. 23.5 mm, IQR 21.0–25.0 mm; P = 0.004), while a smaller diameter was noted at the right common iliac artery (14.0 mm, IQR 11.0–18.0 mm vs. 16.0 mm, IQR 13.0–20.0 mm; P = 0.050).

Procedure, hospitalization, and 30-day complications

A primary technical success endpoint was met in 86.4% of procedures, and an assisted technical success endpoint in 98.3%, with no appreciable divergence across the study arms. On several perioperative measures, the aggregated diabetic cohort fared worse when compared with the non-diabetic group: the length of hospital stay was greater (3.0 days, IQR 2.0–5.5 days vs. 3.0 days, IQR 2.0–4.0 days) (P = 0.017), the operative time ran longer (100.5 min, IQR 75.5–120.0 min vs. 88.0 min, IQR 71.5–112.0 min) (P = 0.039), and a higher proportion developed in-hospital adverse events (38.0% vs. 23.1%) (P = 0.002). By contrast,

the diabetic subset not receiving metformin experienced a reduced intraoperative blood loss volume (0.0 mL, IQR 0.0–100.0 mL vs. 100.0 mL, IQR 0.0–300.0) (P = 0.020) when measured against the non-diabetic arm **(Table 2)**.

Table 2. Hospitalization and 30-day complication details by subgroup.

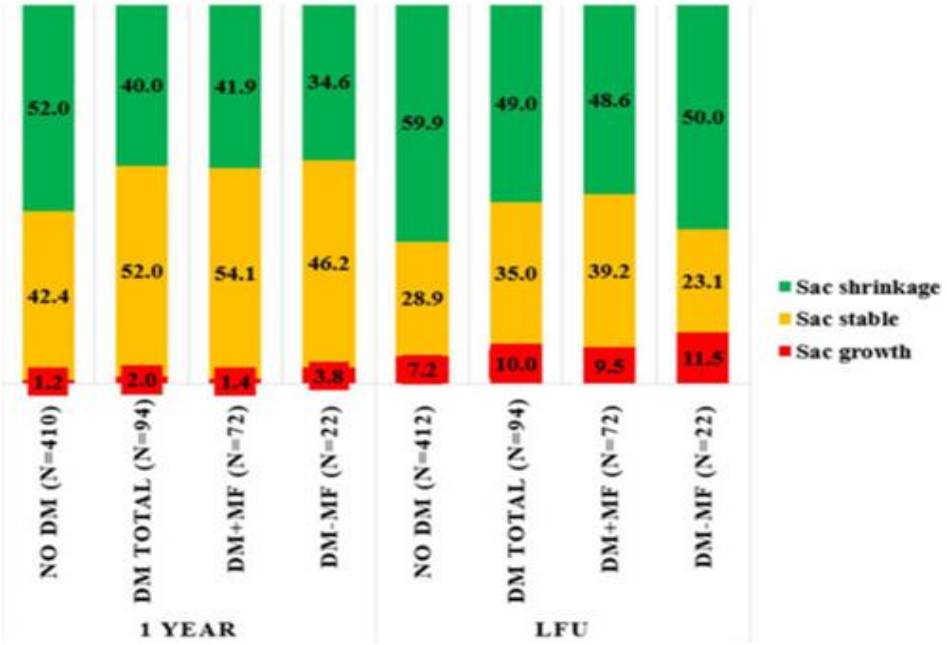
Perioperative outcomes and in-hospital complications by diabetes status							
Variable	**P-value**	**Diabetes without Metformin (n = 26)**	**P-value**	**Diabetes + Metformin (n = 74)**	**P-value**	**Diabetes overall (n = 100)**	**No diabetes (n = 429)**
Length of hospital stay (days)	0.425	3.0 (2.0–5.0)	0.016	4.0 (2.0–6.0)	0.017	3.0 (2.0–5.5)	3.0 (2.0–4.0)
Estimated blood loss (mL)	0.020	0.0 (0.0–100.0)	0.371	150.0 (5.0–300.0)	0.719	100.0 (0.0–250.0)	100.0 (0.0–300.0)
Procedure duration (minutes)	0.474	102.5 (75.0–114.0)	0.039	98.0 (76.0–124.0)	0.039	100.5 (75.5–120.0)	88.0 (71.5–112.0)
Primary technical success	0.071	19 (73.1)	0.087	69 (93.2)	0.602	88 (88.0)	369 (86.0)
Assisted technical success	0.481	25 (96.2)	0.236	74 (100.0)	0.547	99 (99.0)	421 (98.1)
Conversion to open surgery	0.812	0 (0.0)	0.683	1 (1.4)	0.632	1 (3.0)	1 (0.2)
Any in-hospital complication	0.026	11 (42.3)	0.011	27 (36.5)	0.002	38 (38.0)	99 (23.1)
Breakdown of in-hospital complications							
Complication type	**P-value**	**DM without Metformin**	**P-value**	**DM + Metformin**	**P-value**	**Diabetes overall**	**No diabetes**
Systemic complications (total)	—	4 (36.4)	—	4 (14.8)	—	8 (21.0)	31 (31.1)
Urinary tract infection	—	—	—	1 (3.7)	—	1 (2.6)	2 (2.0)
Renal impairment	—	1 (9.1)	—	—	—	1 (2.6)	7 (7.1)
Fever	—	2 (18.2)	—	3 (11.1)	—	5 (13.2)	20 (20.2)
Pulmonary complications	0.643	1 (9.1)	0.250	4 (14.8)	0.499	5 (13.2)	13 (13.5)
Cardiac complications	0.302	1 (9.1)	0.872	6 (23.1)	0.505	7 (18.4)	19 (19.8)
Specific cardiac events							
Event	**DM without Metformin**		**DM + Metformin**		**Diabetes overall**		**No diabetes**
Angina (NYHA class)	—		—		—		1 (1.0)
Myocardial infarction	1 (9.1)		—		1 (2.6)		3 (3.0)
Coronary artery disease	—		—		—		1 (1.0)
Atrial fibrillation	—		—		—		5 (5.1)
Acute heart failure	—		1 (3.7)		1 (2.6)		2 (2.0)
Procedure-related mortality							
Outcome	**DM without Metformin**		**DM + Metformin**		**Diabetes overall**		**No diabetes**
Procedure-related deaths	—		—		—		10 (2.3)

Abbreviations: No DM = individuals free of diabetes mellitus; DM-total = the full set of individuals with diabetes mellitus; DM + MF = individuals with diabetes mellitus who are on metformin; DM-MF = individuals with diabetes mellitus who are not on metformin. P = P-value relative to the non-diabetic reference group. Data are displayed as mean ± SD, count (percentage), or median (Q1; Q3).

Sac remodeling

Viewed across the entire study population, aneurysm sac shrinkage was documented in 49.7% of individuals at the one-year follow-up assessment, rising to 57.8% by the latest available follow-up. At the one-year mark, the proportion of diabetic subjects exhibiting sac shrinkage was 40.0%, compared with 52.0% among subjects without diabetes (P = 0.038). At the same time, a tendency toward greater stability in sac dimensions was evident in the diabetic cohort relative to the non-diabetic cohort (52% vs. 42%; P = 0.055). The fraction of patients showing sac shrinkage did not differ meaningfully when diabetic individuals on metformin were compared with diabetic individuals not prescribed the drug **(Figure 2)**. At the most recent follow-up encounter, sac shrinkage was present in 49.0% of diabetic patients and in 59.9% of non-diabetic

patients (P = 0.067). Sac shrinkage rates proved significantly lower among metformin-treated diabetic patients than among non-diabetic patients (48.6% vs. 59.9%; P = 0.047). No significant differences in sac remodeling outcomes were observed when diabetic patients taking metformin as monotherapy were compared with those whose management did not include metformin — this was true at both the one-year and final follow-up evaluations.



a)

Group	1 year	P vs No DM	P DM+MF vs DM-MF	LFU	P vs No DM	P DM+MF vs DM-MF
DM total	growth	0.497		growth	0.318	
	stable	0.055		stable	0.179	
	shrinkage	0.038		shrinkage	0.067	
DM+MF	growth	0.905	0.369	growth	0.522	0.602
	stable	0.080	0.934	stable	0.086	0.269
	shrinkage	0.076	0.859	shrinkage	0.047	0.455
DM-MF	growth	0.194		growth	0.299	
	stable	0.351		stable	0.778	
	shrinkage	0.217		shrinkage	0.757	

b)

Figure 2. Sac remodeling at the one-year mark and at the last follow-up: (a) Distribution of aneurysm sac shrinkage, stability, and expansion, expressed as percentages, across the various study groups at the one-year and last follow-ups. Due to missing data, the sum of the percentages does not equal 100%; (b) p-values derived from Pearson chi-square tests evaluating sac-related outcomes (shrinkage, stability, and growth) between diabetic and non-diabetic AAA patients, and between diabetic patients receiving metformin and those not receiving metformin. Abbreviations: No DM = subjects without diabetes mellitus, DM total = all subjects with diabetes mellitus, DM + MF = subjects with diabetes mellitus treated with metformin, DM-MF = subjects with diabetes mellitus not treated with metformin, LFU = last follow-up, P = P-value.

The Cox regression model examining drivers of sac shrinkage indicated that higher ASA class, older age, and larger baseline AAA maximal diameter were independently associated with a greater likelihood of achieving sac shrinkage. Working in the opposite direction, a history of hyperlipidemia, identification of an endoleak at any stage during the surveillance phase, and undergoing a reintervention each correlated with a reduced probability of sac shrinkage. The magnitude of these associations, however, was limited. The specific endoprosthesis implanted did not affect the sac's remodeling. None of the additional aneurysm-related covariates emerged as having a statistically robust link to sac shrinkage.

Secondary endpoints

The proportion of patients in whom an endoleak of any classification was initially discovered during the observation period is displayed in **Figure 3a**, stratified by

the one-year landmark and the last available follow-up assessment. Aggregating all groups, an endoleak of some description was present in 22.3% of individuals at the one-year mark and had climbed to 32.7% by the final follow-up. No statistically significant intergroup differences were observed, and across all subgroups, the detection rate increased with longer follow-up **(Figure 3a)**.

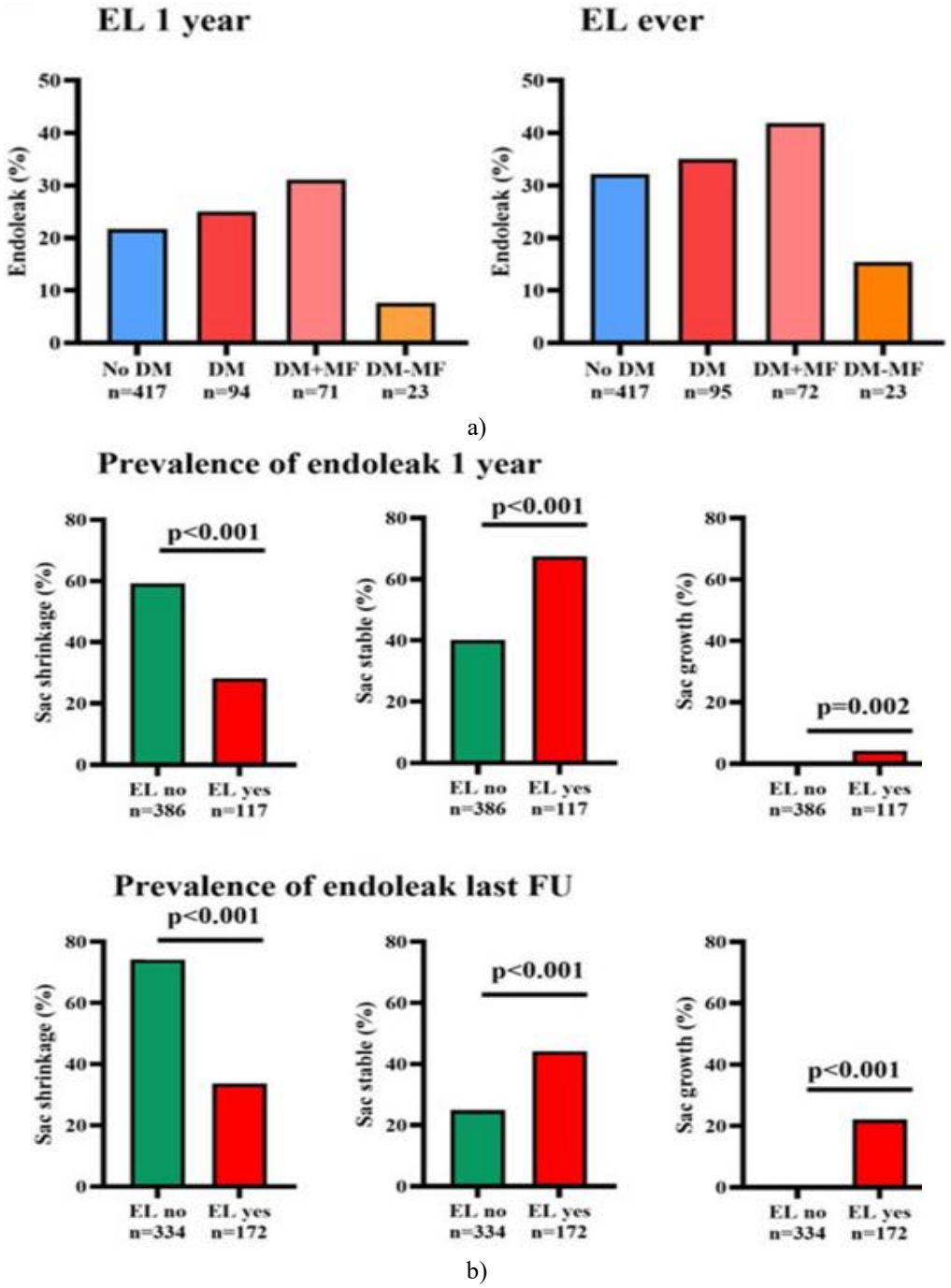
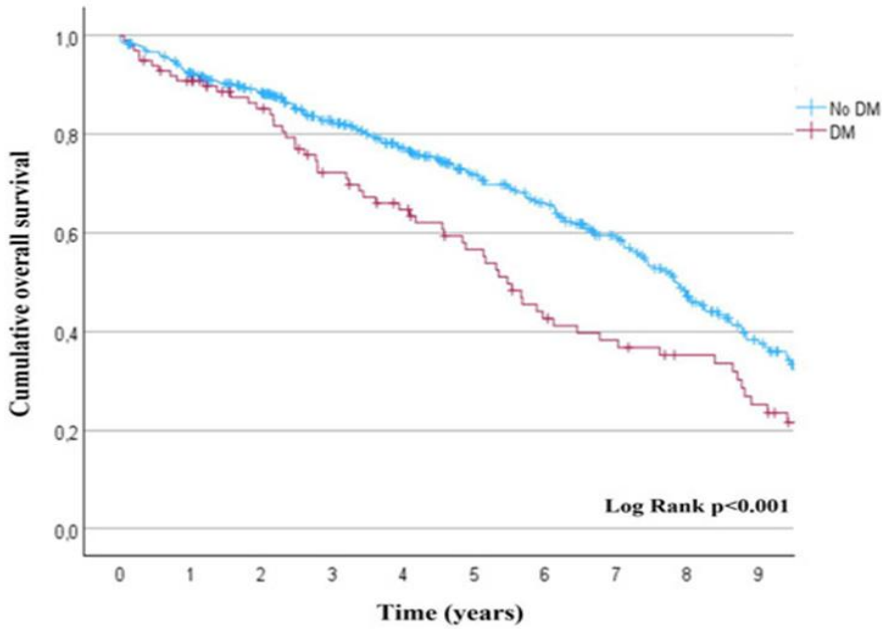


Figure 3. Frequency of endoleak detection at one year post-procedure and at the concluding follow-up visit: (a) Proportion of patients within each study arm in whom an endoleak was identified, shown for both the one-year mark and the final follow-up, with values given as percentages; (b) Distribution of sac remodeling categories, sorted by presence or absence of an endoleak, at the one-year and final follow-up assessments. Remodeling outcomes are depicted as percentage shares within the endoleak-positive and endoleak-negative subsets; listed p-values denote the degree of statistical separation in sac remodeling patterns between patients with and without a detected endoleak, based on the Pearson Chi-square test. Abbreviations: No DM = subjects free of diabetes mellitus, DM total = the complete set of diabetic subjects, DM + MF = diabetic subjects managed with metformin, DM-MF = diabetic subjects managed without metformin, LFU = last follow-up, EL = endoleak, P = P-value.

The distribution of sac remodeling categories according to whether an endoleak was documented or absent is set out in **Figure 3b** for both the one-year and final follow-up time points. On both occasions, endoleak presence heavily outweighed endoleak absence within the subsets characterized by sac stabilization and sac enlargement (P < 0.002). Conversely, among the aneurysms that demonstrated a shrinkage response, an endoleak was encountered at a markedly lower frequency than in the absence of a shrinkage response (P < 0.001 for both assessment moments).

Analysis of reintervention-free survival was capped at the five-year follow-up boundary because, beyond that point, the diabetic subgroup contained fewer than 10 patients. At the five-year time point, the proportion of patients who remained free from reintervention was 75.7% (95% CI: 5.4–6.5) within the diabetic cohort and 81.1% (95% CI: 8.5–9.4) within the non-diabetic cohort (P = 0.355). The inter-subgroup comparisons did not produce any statistically meaningful findings. Over the entire follow-up period, 100 patients (18.9%) underwent at least one reintervention; of these, 38 (7.2%) occurred within the first postoperative year, with subgroup differences remaining non-significant. In 75 cases, a solitary reintervention proved sufficient. Several patients, however, underwent multiple subsequent procedures: 13 patients received two reinterventions, eight received three, three received four, and one patient underwent five. The median interval to the first such procedure was 25 months (IQR = 2.5–58.7 months). For diabetic patients, the median time to first reintervention was 5.3 months (IQR = 1.5–50.9 months), while for the non-diabetic group it reached 26.5 months (IQR = 3.0–61.8 months) (P = 0.295).

At the one-year follow-up, the overall survival rate was 90.8% (95% CI: 29.1–32.9) for diabetic patients versus 92.4% (95% CI: 36.0–37.9) for non-diabetic patients (P = 0.574). The graphical Kaplan–Meier analysis was terminated at 9 years of follow-up because the diabetic arm had fallen below 10 beyond that interval. Through the entire nine-year span, overall survival among diabetic individuals stood at 23.5% (95% CI: 4.7–6.2), in contrast to 37.5% among non-diabetic individuals (95% CI: 7.3–8.4) (P < 0.001) **(Figure 4)**. At the median follow-up duration of 3.8 years, death had occurred in 247 patients (46.7% of the enrolled cohort). Aneurysm-attributable mortality was confirmed in five cases: four occurred in the non-diabetic population and one in a diabetic patient. Regarding the non-diabetic subset, the timing of these aneurysm-related deaths was distributed as follows: one patient on the day of the original procedure, two patients at four days post-procedure, and one patient at five days post-procedure. The single aneurysm-related fatality in the diabetic group took place 50 days after the operation.



	Years	0	1	2	3	4	5	6	7	8	9
No DM											
	N cumulative events		32	48	70	86	101	116	131	153	167
	N at risk	429	384	339	277	232	183	155	119	80	48
	Overall survival (%)	100.0	92.4	88.4	82.2	77.2	71.8	65.7	59.0	47.2	37.5
	SE		0.013	0.016	0.019	0.022	0.024	0.027	0.029	0.033	0.035
DM											
	N cumulative events	1	9	14	26	31	38	47	51	53	59
	N at risk	99	86	73	58	49	40	29	25	20	14
	Overall survival (%)		90.8	85.2	71.0	64.8	55.2	42.6	36.8	33.6	23.5
	SE		0.029	0.037	0.048	0.052	0.055	0.056	0.056	0.055	0.052

Figure 4. Kaplan–Meier plots depicting overall survival. Overall survival throughout a nine-year surveillance window following endovascular aneurysm repair, contrasting non-diabetic individuals with diabetic individuals. Abbreviations: No DM = subjects without diabetes mellitus, DM total = all diabetic subjects, SE = standard error, p signifies the aggregate P-value derived from comparing diabetic patients, both those on metformin and those not on metformin, against patients without diabetes.

The present observational, retrospective cohort analysis demonstrated that, at 1 year following elective EVAR, diabetic patients exhibited less pronounced sac shrinkage than their non-diabetic counterparts, along with a tendency toward greater sac stabilization. By the last available follow-up, sac shrinkage remained 10.9 percentage points higher in the non-diabetic arm, but this margin no longer met the threshold for statistical significance. Notably, at this final follow-up point, diabetic individuals receiving metformin had a significantly smaller proportion of sac shrinkage when compared to the non-diabetic group. Additionally, endoleak detection increased over the surveillance period and was associated with attenuated sac shrinkage at both the one-year and final assessments. Overall survival was substantially worse among diabetic patients, whereas reintervention-free survival and freedom from aneurysm-related death did not diverge meaningfully between the groups.

An inverse association between type 2 diabetes and the prevalence, expansion, and rupture of AAA has been documented in earlier literature [4, 5]. That said, investigations into the impact of DM on post-EVAR outcomes have yielded conflicting results.

Concentrating on the early postoperative period, our results indicated that DM was associated with longer hospital stays, longer procedural times, and a higher rate of in-hospital adverse events. Suboptimal blood glucose regulation is recognized as a contributor to inferior surgical outcomes, encompassing heightened infection rates, impaired wound repair, elevated mortality, and extended inpatient stays [20]. These observations highlight the essential nature of rigorous perioperative glycemic control during the EVAR hospitalization.

A nationwide Swedish observational cohort study that applied propensity score adjustment to compare 748 patients with DM with 2630 without detecting any disparity in all-cause or cardiovascular mortality. Over the course of four years, however, the DM arm experienced fewer reinterventions and an elevated incidence of acute myocardial infarction. Importantly, that investigation did not incorporate an analysis of sac remodeling — spanning growth, stability, and shrinkage — nor did it account for the frequency or classification of endoleaks [21]. In a separate report, diabetic individuals demonstrated lower rates of post-EVAR sac expansion over a 4-year surveillance period, with a trend toward fewer subsequent interventions. Within that same study, neither mortality nor endoleak detection rates differed between diabetic and non-diabetic groups [22]. A more contemporary study assessed sac remodeling over 5 years of follow-up after EVAR among patients implanted with a Gore Excluder endograft and found no intergroup difference in sac regression, identifying only an elevated 5-year mortality rate among diabetic patients. This finding held after adjustment for concomitant comorbidities [23]. Furthermore, a meta-analysis designed to identify and weigh factors influencing sac shrinkage after EVAR reported a trend toward reduced shrinkage in patients with DM [1].

The studies cited above limited their scope to the effects of DM, without accounting for metformin treatment. Our data showed that at the last follow-up — at a median of 3.8 years — sac shrinkage was significantly lower among diabetic patients taking metformin than among non-diabetic patients. It must be acknowledged that the diabetic subgroup not prescribed metformin comprised a relatively small number of patients. Offering a counterpoint, a comparable single-center study concluded that metformin intake does not appear to exert a meaningful influence on long-term AAA sac remodeling following EVAR [24]. Given the divergent findings concerning how diabetes and metformin use shape post-EVAR endpoints — including sac remodeling and overall survival — further research is warranted.

Drawing upon the body of evidence reviewed above, it would seem that while individuals with diabetes may be partially protected against sac enlargement over time, there exists no parallel evidence indicating that DM confers any benefit on sac shrinkage after EVAR. A variety of structural and molecular alterations documented within the aortic wall of diabetic patients may help account for this seeming paradox. Where AAA patients typically display depletion of the aortic wall matrix, those with DM frequently exhibit an expanded vascular matrix compartment [25]. Moreover, collagen production is upregulated in the diabetic state, thickening the aortic wall while concomitantly suppressing matrix metalloproteinase (MMP) levels, the enzymes that degrade extracellular matrix (ECM) components. Concurrently, the hyperglycemic and hyperinsulinemic environment characteristic of DM drives the accumulation of advanced glycation end products (AGEs). These AGEs establish cross-links with the collagen and elastin framework of the aortic wall and stimulate vascular SMC proliferation, culminating in a vessel wall that is both more resistant and mechanically stronger [26]. This cascade is thought to

underpin the diminished risk of AAA. At the same time, the resultant increase in aortic wall stiffness may also explain why, after EVAR, diabetic patients exhibit less sac shrinkage and a trend toward greater sac stabilization than those without diabetes.

Hyperlipidemia was encountered more frequently among diabetic individuals than among non-diabetic individuals. In the Cox regression framework, it emerged as a factor inversely associated with sac shrinkage, albeit with a small effect size. Other baseline comorbidities — namely, hypertension, body mass index, a history of cardiac disease, and preoperative glucose concentrations — did not emerge as meaningful predictors of sac shrinkage when the full cohort was evaluated. In keeping with our observations, a broad-scope meta-analysis of patients undergoing endovascular aneurysm repair likewise failed to establish any connection between comorbidities such as hypertension, obesity, and coronary artery disease and the likelihood of postoperative sac shrinkage [1]. Of interest, that same meta-analysis reported that hypercholesterolemia exerted a favorable influence on sac shrinkage, and a potential trend linking sac shrinkage with statin therapy was also noted. For these reasons, clustering of these comorbidities within the diabetes mellitus group may not fully explain the blunted sac shrinkage observed here.

Metformin has been hypothesized to modulate the natural course of AAA [9], and several RCTs have been initiated to test this hypothesis in patients with small aneurysms. Preclinical work in animal models has associated metformin administration with suppressed AAA initiation and progression, along with preservation of medial elastin and aortic SMCs, dampened infiltration of inflammatory cells, and reduced neovascularization [10, 11]. These pharmacological actions may well be protective against aneurysmal expansion, yet they are not necessarily conducive to promoting sac shrinkage. At both the one-year time point and the concluding follow-up, the rate of sac growth was numerically lower, and the proportion of stable sac behavior numerically higher, in the metformin-exposed diabetic subgroup compared with the diabetic subgroup not receiving metformin. These differences, however, did not reach statistical significance. In addition, a recent study found that diabetic patients were more likely to demonstrate sac stability. In contrast, non-diabetic patients were more likely to experience sac regression at 1 year after EVAR [27]. That study further reported that diabetic patients managed with non-insulin antidiabetic agents carried a reduced risk of post-EVAR rupture.

Within our dataset, endoleaks — irrespective of classification — increased in frequency over time and were consistently associated with less pronounced sac shrinkage at both the one-year mark and the final follow-up. The Cox regression analysis further confirmed that documented endoleak was significantly and independently associated with diminished sac shrinkage. These results align with those of an earlier meta-analysis, which likewise identified endoleak presence as a correlate of reduced sac regression following EVAR [1]. Taken together, these findings reinforce the critical importance of close surveillance and proactive endoleak management throughout post-EVAR follow-up.

A substantial survival disadvantage was apparent among diabetic patients — both those taking metformin and those not — when tracked across a nine-year follow-up window and compared against non-diabetic patients. This observation is in agreement with a prior study that paired diabetic patients with non-diabetic controls of comparable age and comorbidity status [23], with a recent large observational series encompassing eight years of follow-up [27], and with a meta-analysis aggregating 12 cohort studies that collectively included 20,210 individuals who underwent AAA repair [28]. At the same time, these results stand in contrast to reports from other investigations, which found that diabetes had no bearing on overall mortality [21, 22]; critically, those studies featured shorter follow-up durations, and in the initial years following EVAR, our own data similarly showed no mortality divergence between groups. Since reintervention-free survival and freedom from aneurysm-related death did not differ between diabetic and non-diabetic patients, the focus must shift toward rigorous glycemic control and the aggressive management of concomitant conditions — particularly the optimization of cardiovascular risk profiles in the diabetic population — as a strategy to improve long-term survival.

Several methodological shortcomings in the present study warrant acknowledgment. First, aneurysm sac measurements were taken from whichever imaging modality was available—CTA or DUS. These two modalities do not yield measurements that can be directly substituted for one another. Still, the discrepancy in determining the mean aortic diameter in patients with aneurysmal disease is recognized to be less than 5 mm [29]. As stipulated by current guidelines, the 30-day postoperative scan was invariably a CTA, following which long-term imaging surveillance is recommended for all EVAR recipients [30]. At our institution, DUS was the favored modality for extended follow-up. As such, the majority of scans from the one-year mark onward through to the last recorded follow-up were performed using the same imaging technique.

A further constraint arises from the retrospective design, which relied on a manually populated database. Such a structure is inherently vulnerable to both data entry errors and missing data points. The interval between the initial diagnosis of diabetes and the commencement of metformin therapy to the point of study inclusion was unknown, and these temporal variables could well have

influenced the observed outcomes—an angle worthy of investigation in future studies.

An additional limitation stems from the marked asymmetry in subgroup sizes, a problem that particularly afflicts the diabetic arm not taking metformin. As the number of patients remaining at risk thinned out over extended follow-up, assumptions of normality and homogeneity of variance were undermined. Although non-parametric analytic approaches were deployed to partially address this difficulty, statistical power was nonetheless compromised. The considerable dispersion in follow-up durations further complicated temporal analyses extending to the last follow-up date; it is worth noting, however, that follow-up length did not systematically differ between the study groups. Furthermore, only a tiny fraction of the diabetic patients in the cohort were taking metformin as their sole glucose-lowering agent. When comparisons were drawn between diabetic patients on metformin monotherapy and those not on metformin at all, sac remodeling patterns proved indistinguishable at both time points. Owing to the limited number of individuals receiving only metformin, we deliberately decided to differentiate diabetic patients solely by the presence or absence of metformin in their treatment regimen. Other antidiabetic agents — including sulfonylurea derivatives and insulin — may have confounded the results. That said, we formally tested sulfonylurea use as a candidate predictor of sac shrinkage within a Cox regression framework and found no significant effect. Moreover, prior observational studies have identified only metformin as having a significant effect on AAA enlargement [7, 8]. It would also have been preferable to report HbA1c values rather than isolated glucose levels as a more faithful indicator of chronic glycemic status, yet HbA1c measurements were available for only roughly half of the study population. There is also the matter of the many baseline characteristics that differed between groups and influenced both sac remodeling and overall survival. Finally, the ten years covered by this study cannot be overlooked as a potential source of variation; as institutional and operator experience accrued, procedural success rates may well have improved over time, perhaps introducing an era effect.

Conclusion

In sum, this retrospective study documents a negative relationship tying diabetes mellitus and metformin use to aneurysm sac shrinkage following EVAR. Diabetic patients demonstrated significantly less sac shrinkage than non-diabetic patients at one-year follow-up. At that same juncture, however, a trend toward more frequent stabilization of sac dimensions was observed in the diabetic cohort. By the last follow-up, only the subgroup of diabetic patients receiving metformin continued to exhibit lower sac shrinkage rates than the non-diabetic group. Separately, endoleak prevalence increased over the surveillance interval in both diabetic and non-diabetic AAA populations, and endoleak presence correlated with blunted sac shrinkage at both evaluated time points. These results underscore the essential role of meticulous endoleak monitoring and management during post-EVAR surveillance. Overall survival was significantly curtailed in the diabetic population compared to the non-diabetic population. Yet, reintervention-free survival and freedom from aneurysm-related death did not diverge significantly between the groups. Given the heterogeneous and at times contradictory nature of the published evidence on this topic, further prospective multicenter studies are urgently needed to clarify the precise influence of diabetes and metformin therapy on post-EVAR outcomes.

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Ethics statement: Ethical review was waived for this study by the medical ethics committee, and the local board of directors of Rijnstate Hospital approved the study due to the use of anonymized patient information retrieved from medical records [16141 on 11 January 2023 and 2183 on 25 January 2023, respectively].

The institute's opt-out registry was consulted to determine whether or not patients objected to participating in scientific research.

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