Autologous venous vascular reconstruction compared to non-autologous reconstruction as surgical treatment for vascular infections in vascular chronic Q fever patients

Written report

Jesper M. Weehuizen
Olivierdreef 10
3562LJ Utrecht
Student number: 3858804
Email: j.m.weehuizen@students.uu.nl
Private email: jesperweehuizen@outlook.com

Utrecht University
Faculty: Medicine
Graduate school: Life science
Programme: Epidemiology Postgraduate

Daily supervisor: Dr. J.J. Oosterheert
Examiner: Dr. C.H. van Werkhoven
Second reviewer: Dr. P.C.J. Bruijning-Verhagen

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Nederlandse samenvatting:

Tussen 2007-2010 heeft Nederland te maken gehad met de grootste Q-koorts uitbraak wereldwijd. Q-koorts is een infectieziekte veroorzaakt door de bacterie *Coxiella burnetii* en wordt meestal overgedragen van geiten of schapen op mensen. De meeste personen die in aanraking komen met de bacterie krijgen griepachtige verschijnselen of een longontsteking, waarna de bacterie weer uit het lichaam verdwijnt. Bij een klein gedeelte van de geïnfecteerde mensen (1-5%) kan de bacterie in het lichaam aanwezig blijven. De bacterie gaat dan vaak op een hartklep of de aorta zitten, met name als die persoon door een eerdere operatie al een prothese heeft aan de hartklep of aorta. Als hier sprake van is, noemen we het chronische Q-koorts. Chronische Q-koorts kan ernstige gevolgen hebben. Het kan leiden tot een gescheurde aorta en zelfs tot de dood. In dit onderzoek focussen we op de groep chronische Q-koorts patiënten met een infectie aan de aorta.

Om te voorkomen dat iemand met een geïnfecteerde aorta ernstige complicaties krijgt, behandelen we diegene langdurig met antibiotica. Daarnaast kan je diegene opereren. Momenteel is het alleen niet duidelijk welke operatie het beste werkt; het gebruik van kunstmateriaal of eigen materiaal. Het gebruik van eigen materiaal is een relatief nieuwe methode waarbij ze een ader uit het been omvormen en hier de aorta mee vervangen. Een groot voordeel van eigen materiaal ten opzichte van kunstmateriaal is dat eigen materiaal minder snel opnieuw geïnfecteerd raakt met een bacterie.

In de afgelopen jaren is informatie over alle chronische Q-koorts patiënten in Nederland opgeslagen in de Nationale Chronische Q-koorts Database. Hieruit zijn alle patiënten met een operatie aan een geïnfecteerde aorta of vaatprothese geselecteerd. Daarna is gekeken welk type operatie zij hebben gehad: 27 operaties met eigen materiaal (beenader) en 63 operaties met kunstmateriaal. Deze twee groepen zijn, na correctie, vergeleken door middel van een survival analyse. Hieruit bleek dat personen die een operatie hebben gehad met eigen materiaal minder complicaties hebben en de bacterie beter uit het lichaam verwijderd werd dan bij de personen met kunstmateriaal.

Het is belangrijk om te beseffen dat de patiënten in dit onderzoek niet willekeurig zijn ingedeeld in één van de twee groepen, zoals je het liefst hebt bij het onderzoeken welke behandeling het beste is voor een ziekte. De toenmalig behandelend arts heeft bepaald wat voor type operatie iemand kreeg. Het is dus mogelijk dat artsen met name ziekere en/of oudere patiënten met kunstmateriaal hebben behandeld, terwijl deze groep sowieso vaker complicaties krijgt na een operatie. In deze studie hebben we hier zoveel mogelijk voor geprobeerd te corrigeren. Volledig corrigeren is echter niet mogelijk.

In dit onderzoek concluderen we dat chronische Q-koorts patiënten met een geïnfecteerde aorta het beste geopereerd kunnen worden met eigen materiaal vanuit, mits een patiënt hiervoor in aanmerking komt.

Abstract

Background: There is no consensus on the preferred type of surgical intervention for an infected abdominal aneurysm or infected vascular prosthesis caused by *Coxiella burnetii* in chronic Q fever (CQF) patients. Autologous venous vascular reconstruction is an attractive surgical treatment option, but comparative research is lacking.

Methods: We compared autologous venous vascular reconstructions with non-autologous reconstructions in a cohort of proven vascular CQF patients. Patients with infected (endo-)vascular grafts as well as primary infected abdominal aortic aneurysms were included. Primary outcome was vascular chronic Q fever-related events. Secondary outcomes were all-cause mortality, vascular chronic Q fever-related mortality, and vascular chronic Q fever recurrence.

Results: In total, 81 patients with 90 vascular reconstructions were included in the study. Autologous reconstructions were performed in 27 (30.0%) cases and non-autologous reconstructions in 63 (70.0%) cases. The median follow-up time was 37.5 months (Interquartile range: 9.8 – 69.0 months). The risk of early all-cause mortality, Q fever-related mortality (adjusted hazard ratio (HR) both: 1.82 95% CI 0.39 – 7.84) and Q fever-related events (HR 1.46 95% CI 0.33 – 5.83) were not different. The adjusted HR for late Q fever-related events was 0.08 (95% CI 0.02 – 0.43) and for vascular chronic Q fever recurrence 0.12 (95% CI 0.03 – 0.44). No significant differences were observed for the risk of late all-cause mortality (HR 0.67 95% CI 0.22 – 2.06) and late Q fever-related mortality (HR 0.14 95% CI 0.01 – 1.47).

Conclusion: Autologous venous reconstructions for vascular infections in proven CQF results in less late Q fever-related events compared to non-autologous reconstructions.

Keywords

Vascular infection; autologous venous vascular reconstruction; vascular chronic Q fever; Coxiella burnetii; Dutch Q fever outbreak;

Key Messages

- Use of autologous venous vascular reconstruction results in improved clinical outcomes compared to non-autologous reconstruction in vascular chronic Q fever patients
- The findings in this study could possibly be extrapolated to vascular infection by other infective pathogens.

Introduction

Q fever is a zoonosis, caused by the intracellular bacterium *Coxiella burnetii*.(1) Chronic infection with *C. burnetii* predominantly infects heart valves, large blood vessel walls, or vascular prostheses, causing chronic Q fever (CQF) endocarditis or vascular CQF, and has a high morbidity and mortality(2,3). The largest Q fever outbreak worldwide took place in the Netherlands between 2007 and 2010, with approximately 40.000 - 50,000 persons infected(4). Before the Dutch outbreak, the main known presentation of CQF was endocarditis. A vascular focus of infection was only seen in around 25% of CQF patients(5,6). However, data from the Dutch National Chronic Q fever Database showed CQF patients in the Netherlands predominantly have a vascular focus of infection(>65%)(7). In vascular CQF patients, infection of the vascular wall or prosthetic material is frequently observed and often the cause of complications such as aorto-enteric fistulas, aneurysm rupture, abscess formation and vertebral osteomyelitis(2,3).

There is no consensus in medical literature on the preferred type of surgical intervention for an infected abdominal aneurysm or infected vascular prosthesis in general. A well-known method is removal of infected graft material and local debridement followed by an extra-anatomical bypass via a non-infected route(8). The risk of a fatal aortic stump blow-out is however high, and an in situ reconstruction is therefore considered as more advantageous(8,9). Endovascular Aneurysm Repair (EVAR) to treat vascular (graft) infections appear to have only short-term advantages in an acute setting or as bridge to further surgery. In the long term, endovascular reconstructions are associated with a higher risk of infection-related complications, reoperation, and readmission rate(10,11). Autologous venous vascular in situ reconstruction, using the femoral vein or the greater saphenous vein, is an attractive surgical treatment option for abdominal vascular infections as it avoids using prosthetic material(12–14). However, comparative research between autologous venous vascular reconstruction and non-autologous reconstruction in a cohort of patients with an abdominal vascular infection is lacking.

In this study, we aim to evaluate surgical interventions for infected aneurysms or infected vascular prostheses by comparing autologous venous vascular reconstruction with non-autologous vascular reconstruction for an infected abdominal aneurysm or vascular prostheses in vascular CQF patients.

Methods

Study population and data collection

A retrospective nationwide cohort of CQF patients was established after the Dutch Q fever outbreak. This database included all known patients with CQF from participating hospitals in the Netherlands, since the start of the outbreak in January 2007 until December 2020. Data on patient and disease characteristics, including clinical, microbiological, and radiological data, were collected from the electronic medical records and stored in the Dutch National Chronic Q Fever Database. Further details of this initiative have been reported previously(2,7,15). For this study, patients diagnosed with proven vascular CQF were selected from the database. Diagnosis of CQF was based on predefined criteria (16)**(Supplementary Table 1)**.

Microbiological analysis

C. burnetii phase I and II IgM and IgG antibody titers were measured in routine clinical practice using indirect immunofluorescence antibody assay with dilutions on a binary scale (Focus Diagnostics, Cypress, CA, USA, or Fuller Diagnostics, LLC, Anchorage, AK, USA). A cutoff of 1:32 was deemed positive. Real-time PCR was performed on serum, blood, or tissue samples retrieved from patients (in-house laboratory-developed test, targeting the transposase gene present in the multicopy IS1111 repetitive element)(17).

Vascular surgical intervention

Proven CQF patients with an infected aorto-iliac aneurysm or infected abdominal vascular graft were included. Autologous venous reconstructions were performed with either the femoral vein (Nevelsteen procedure) or by spiral vein reconstruction using the greater saphenous vein. Non-autologous reconstructions included EVAR, in situ vascular reconstructions using stent grafts of prosthetic matieral or biografts, and extra-anatomic bypasses. An aneurysm or vascular graft infected with *C. burnetii* is not always recognized clinically before intervention. Patient without an clinically recognized infection were surgically treated because of a large asymptomatic aneurysm, symptomatic aneurysm, or endoleak of current graft. Therefore, we divided the indication for vascular reconstructions in three groups: Aneurysm or vascular graft without a clinically recognized infection, infected aneurysm or vascular graft without abscess or fistula, infected aneurysm or vascular graft with abscess or fistula. Patients with a ruptured aneurysm were excluded, because autologous reconstruction is not possible for this indication. Furthermore, vascular reconstructions could be performed electively, planned during an outpatient visit, or as emergency surgery short after an emergency department visit.

Clinical outcomes

Complications and mortality were defined as probably or definitely related to CQF by predefined criteria**(see Supplementary Text)**. Assessment of CQF-related complications and mortality was performed by two authors (J.W. and C.B.) and discordances discussed until consensus was reached. The primary outcome was the occurrence of a vascular CQF-related event, either, vascular CQF-related complication, vascular CQF-related surgical (re-)intervention, or CQF-related mortality. Definitions of vascular CQF-related complications and mortality are listed in the **Supplementary Text.** Secondary outcomes were all-cause mortality, CQF-related mortality, and vascular CQF recurrence, defined as a new vascular CQF-related event 3 months after the intervention and/or a new positive PCR on serum/blood after having been negative for at least 3 months and/or a persistent positive PCR on serum/blood for more than 6 months during antibiotic treatment.(7,18)

Statistical analyses

Data were exported from a Microsoft Access database (version 2013, Microsoft, Redmond, WA, USA), via SAS (SAS Institute Inc., version 9.4, Cary, North Carolina, USA) to SPSS (version 26.0.0.1., IBM Corp., Armonk, New York, USA) and R Studio (Version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria). Descriptive data were generated using SPSS and analyses were performed using R Studio.

A survival analysis using a Cox regression analysis was not possible because the assumption of proportional hazards did not hold for the entire follow-up time. The hazard ratio in the first three months was different from the hazard ratio three months after the intervention. Therefore, we chose to study early (≤3 months after intervention) and late (>3 months after intervention) chronic Q fever related-events separately.

For the analysis of early CQF -related events, a Cox-regression analysis was performed for the primary outcome and the secondary outcomes all-cause mortality and vascular CQF-related mortality. Determinant of interest was autologous venous vascular reconstruction vs. non-autologous vascular reconstruction. Firth's correction was used to correct for bias of maximum likelihood due to small sample size and unbalanced covariates.

The analysis of late vascular chronic Q fever-related events was performed using a Cox-regression for the primary outcome and the secondary outcomes all-cause mortality, vascular CQF -related mortality, and vascular CQF recurrence. To account for informative censoring due to competing risk in the primary outcome and the secondary outcomes vascular CQF -related mortality and vascular CQF recurrence, we performed a second survival analysis using a stratified Fine and Gray model with the same covariates and stratification variable.

The following covariates were added to the both the early and late model to account for possible confounding based on previous studies on Q-fever related complication and mortality(2,24): age at

intervention, comorbidities (diabetes mellitus ischemic cardiac disease, chronic obstructive lung disease, chronic kidney failure and immunocompromised state), positive *C. burnetii* PCR on serum/blood or tissue at any time before intervention, elective or emergency surgery, a native aneurysm repair or graft replacement/repair, and a dichotomous variable if the intervention took place before or at time of diagnosis of CQF, or more than 1 month after diagnosis. The model was stratified by the indication of the intervention (aneurysm or vascular graft without a clinically recognized infection, infected aneurysm or vascular graft without abscess or fistula, infected aneurysm or vascular graft with abscess or fistula) due to a differences baseline hazard for the different indications. The model remained stable after entering the covariates and stratification variable based on the limited broadening of the standard error. The proportional hazard assumption for the analysis was verified and confirmed with formal tests and graphically using Schoenfeld residuals on both the early and the late Cox regression model.

Patients were censored after their first vascular CQF -related event, because a second vascular CQF -related event is not independent of the first event. If a second vascular surgery was performed in the same patient, with a surgical indication corresponding with the before mentioned indications, that patient was included in the analysis for a second time with a new episode and risk for the outcome. A sensitivity analysis was performed excluding the second intervention in the same patients to assess the robustness of the data on this assumption.

Hazard ratios (HR) were calculated with the stratified cause specific Cox regression analysis and subdistributions hazard ratios (SHR) were calculated using the stratified Fine and Gray model. The Cox proportional hazards models were fit with the "survival" package and the stratified Fine and Gray model was fit with the "crrCS" package in R.

Subgroup analysis

In situ vascular reconstruction has a possibly favorable long-term outcome compared to the use of extra-anatomic bypasses(8). Therefore, a subgroup analysis for late outcomes measures was performed excluding extra-anatomic bypasses.

Results

We identified 585 CQF patients in the participating hospitals. proven CQF was diagnosed in 350 patients (59.8%) of which 239 patients (68.3%) had a vascular focus of infection (**Figure 1).** A vascular surgical intervention was performed 177 times in 141 (59.0%) proven vascular CQF patients. In total, 90 aorta-iliac reconstructions, performed in 81 (33.9%) patients, were included in the analysis. An autologous venous reconstruction was performed 27 times (30.0%) in 27 patients and a non-autologous reconstruction 63 times (70.0%) in 59 patients. Three patients underwent a second non-autologous reconstruction after an initial non-autologous reconstruction, four patients received an autologous reconstruction after their first non-autologous vascular reconstruction, and one patient underwent two non-autologous vascular repairs before an autologous venous vascular reconstruction. The median number of months between the CQF diagnosis and the vascular reconstruction was higher in the autologous reconstruction group compared to the patients with non-autologous reconstruction (6 months (IQR 0-16 months) vs. 0 months (IQR 0-5 months). *C. burnetii* PCR on serum was performed in 100% (n=27) of patients with an autologous venous reconstruction and 85.7% (n= 54) of patients with a non-autologous reconstruction before or during the intervention, of which 13/27 (48.1%) and 32/54 (59.3%) were positive, respectively. A PCR was performed on tissues obtained during 85.2% (n=23) of the autologous venous reconstructions and on tissues obtained during 50.8% (n=32) of the non-autologous reconstructions. Following an EVAR procedure tissue for PCR is often not available. The PCR on tissue was positive in 18/23 (78.3%) of the autologous, and 29/32 (90.6%) of the non-autologous reconstructions. Also, more patients with a non-autologous venous reconstruction had already received antibiotic treatment for CQF before the intervention (77.8% vs. 42.9%). All patients that survived the surgical intervention received antibiotic treatment afterwards (**Table 1).**

<u>Vascular surgical interventions:</u>

Among 90 included abdominal vascular reconstructions, 12 (13.3%) autologous femoral vein reconstructions, 15 (16.7%) spiral vein reconstructions, 26 (28.9%) EVAR, 30 (33.3%) open in situ vascular repairs of which 27 with prosthetic material and 3 biografts, and 7 (7.8%) extra-anatomic bypasses were performed (**Table 1)**. Autologous reconstructions were more often used as a graft replacement or repair compared to non-autologous reconstruction (51.9% vs 22.2%), and were more often performed as elective surgery (77.8% vs. 47.3%). Non-autologous reconstructions were performed in patients with an aneurysm or vascular graft without clinically recognized infection in 27 (42.9%) of the interventions, as compared to 3 (11.1%) in patients that underwent autologous venous vascular reconstruction.

<u>Clinical outcomes</u>

The median follow-up after vascular reconstruction was 37.5 months (IQR, 9.8 – 69.0 months). Eleven (40.7%) patients died after an autologous reconstruction and 32 (50.8%) patients died after non-autologous reconstructions. Thirty-day mortality was 11.1% (n=3) after autologous reconstruction and 7.9% (n=5) after non-autologous reconstructions. Vascular chronic Q fever-related mortality occurred in 5 (18.5%) patients after autologous reconstruction and in 23 (36.5%) of the patients after non-autologous reconstruction. Also, vascular chronic Q fever-related complications occurred more frequently after non-autologous reconstruction (11.1% vs. 34.9%). Furthermore, vascular chronic Q fever-related (re)intervention took place more often after non-autologous reconstruction (3.7% vs. 30.2%). A reinfection or persistent infection with *C. burnetii*, based on a positive *C. burnetii* PCR after a period of at least 3 months of having a negative PCR, or a persistent positive PCR after 6 months of antibiotic therapy occurred less often in patients with an autologous reconstruction compared to those with a non-autologous reconstruction (7.4% vs. 15.9%) (**Table 2).**

No difference was found in our primary analysis for early vascular chronic Q fever related-events between autologous and non-autologous reconstruction (aHR 1.46 (95% CI 0.33 - 5.83)). Furthermore, the hazard of non-autologous reconstruction for all-cause mortality and vascular chronic Q fever-related mortality did not differ from the hazard of autologous reconstruction (HR 1.82, 95% CI 0.39-7.84) for both outcomes).

The hazard of late vascular chronic Q fever-related events was significantly lower after autologous reconstruction (aHR 0.08 (95% CI, 0.02-0.43). Autologous reconstruction was also associated with less vascular chronic Q fever recurrence (aHR 0.12 (95% CI 0.03 – 0.44)) **(Table 3)**. The hazard of late all-cause mortality did not differ between the groups (aHR 0.67 (95% CI 0.22 – 2.06)), just like the hazard for vascular chronic Q fever-related mortality (aHR 0.14 (95% CI 0.01 – 1.47)). Our competing risk analysis using the Fine and Gray model (**Table 3)** and sensitivity analysis excluding the second and third intervention in the same patient (**Supplementary Table 2)** did not change the hazard ratios for either outcome.

The subgroup analysis excluding extra-anatomic bypasses also showed a significant difference in Q-fever related mortality with an adjusted HR of 0.04 (95% CI 0.01 – 0.47). The other outcome measures showed comparable results as the initial analysis. The results from the subgroup analysis are shown in **Supplementary table 3**.

Discussion

In our cohort of patients with vascular CQF, we observed that autologous reconstruction as surgical treatment for an infected abdominal aneurysm or vascular graft resulted in less late vascular chronic Q fever-related events and vascular chronic Q fever recurrence compared to non-autologous reconstruction, while no difference was observed in early mortality and early vascular chronic Q fever-related events.

To our knowledge, this is the first comparative study between autologous versus non-autologous reconstruction as surgical intervention for infected aorto-iliac aneurysms and graft infections in a cohort of vascular CQF patients. Although only patients with vascular CQF were included, these results may have implications for vascular repair strategies in vascular infections caused by other pathogens as well. We structurally collected data since the end of the Dutch Q fever outbreak and important outcome measures were always assessed by more than one researcher. Furthermore, a detailed analysis was performed accounting for known confounders, right censoring, and a difference in baseline hazards. Competing risks and the effect of a potential influential variables were assessed using a sensitivity and subgroup analysis.

Several case series have previously presented long-term follow-up after autologous venous vascular reconstruction. These series reported a post-operative or 30-day mortality of 0 – 15.3%(13,19–22), which is comparable to our study with a 30 day mortality of 11.1%. In our study, 10 patients died (37.0%), of which 5 deaths (18.5%) were Q fever-related in the first 5 years after the reconstruction, which matches the 5-year mortality rate reported in literature of 30% - 40%(19,22). In our study, one patient (3.7%) developed a graft stenosis which was first treated with percutaneous transluminal angioplasty and later an endovascular stent was placed inside the venous reconstruction. Graft stenosis after autologous venous vascular reconstruction is observed in 0 – 20% (13,19,22). Autologous venous vascular reconstruction has the potential for chronic venous morbidity after removal of the leg veins. The Dutch National Chronic Q Fever Database did not include data on chronic venous morbidities. However, chronic venous morbidity has been reported in around 10% of the patients in earlier studies, mostly without the need for further therapy.(19,22,23)

In a meta-analysis, in situ vascular reconstruction has favorable outcomes compared to extra-anatomic bypasses as surgical treatment for abdominal vascular infections.(8) In our subgroup analysis including only in situ vascular reconstructions, we observed also a significant reduction in Q-fever related mortality after autologous venous vascular reconstruction in addition to the initial analysis, supporting the initial conclusion on the findings in this study.

The case series above describes good clinical outcomes for autologous venous vascular reconstructions in infected aneurysms or vascular grafts with other pathogens, mainly *Staphylococcus* or *Enterococcus* species(13,19,22). The favorable results for autologous venous vascular reconstruction in proven vascular CQF patients with a *C. burnetii* infection in this study are in line with the earlier presented case series. Therefore, the results in this study could possibly be extrapolated to infections with other pathogens. However, aorto-iliac vascular infections with *C. burnetiii* have a more chronic course, and therefore comparison with other pathogens must be done with caution.

Although autologous venous vascular reconstruction has a clear advantage over non-autologous vascular reconstruction as surgical treatment in proven vascular CQF patients in this study, it is important to state that this intervention is not feasible for every patient with an abdominal vascular infection. If the condition of the patient is too feeble or unstable for an open abdominal surgical intervention, or if it is not possible to harvest the veins due to pre-existing venous morbidity, (endovascular) placement of a non-autologous graft can still be a good alternative

Our study has several limitations. We performed our analysis on a retrospective database. The choice of autologous or non-autologous in the patients included in this database was done in clinical practice. Several factors contributed to this choice. First, autologous venous reconstruction is not performed in all participating hospitals, which makes the choice partly random and feasible for comparative research. However, patient and disease characteristics also contributing to the choice of vascular reconstruction, which leads to confounding by indication in our analysis. Although we adjusted for known potential confounders, the analysis is still affected by unmeasured confounders due to confounding by indication. Therefore, the effect found in our analysis cannot be totally contributed to difference in surgical treatment, but also to confounding by indication as a consequence of surgical treatment choice by the treating physician. However, the difference in clinical outcomes between autologous and non-autologous reconstructions after adjustment for confounders is substantial. Therefore, it is unlikely that the difference can be totally explained by confounding by indication, and autologous reconstruction still results in better clinical outcomes in vascular CQF patients. Another limitation in our study is the limited sample size due to the rarity of vascular CQF. The difference in Q fever-related mortality was not significant in our analysis, however analysis showed a large point estimate and the non-significance could have been the effect of a large standard error due to a limited sample size. As consequence of the small sample size we weren't able to assess a difference in effect if for example only native aneurysm repairs were included. Also, both the autologous and non-autologous vascular reconstructions have considerable heterogeneity of methods applied for arterial reconstruction. Nevertheless, the Dutch National Chronic Q fever Database harbors the largest cohort

of vascular CQF patients reported in literature, which makes the availability of higher quality data unlikely.

In conclusion, autologous venous vascular reconstructions as surgical intervention for infected abdominal aorto-iliac aneurysms or vascular prosthesis in proven vascular CQF patients resulted in less late Q fever-related events and therapy failure compared to non-autologous reconstruction, without difference in early clinical outcomes.

Declaration of interests

The authors declare no competing interests.

Privacy regulation and ethical approval

The local Medical Ethics Committee of the University Medical Centre Utrecht declared that the study was exempt from ethics review. The internal review board from participating hospitals approved the anonymous processing of data and waived the need for informed consent from patients.

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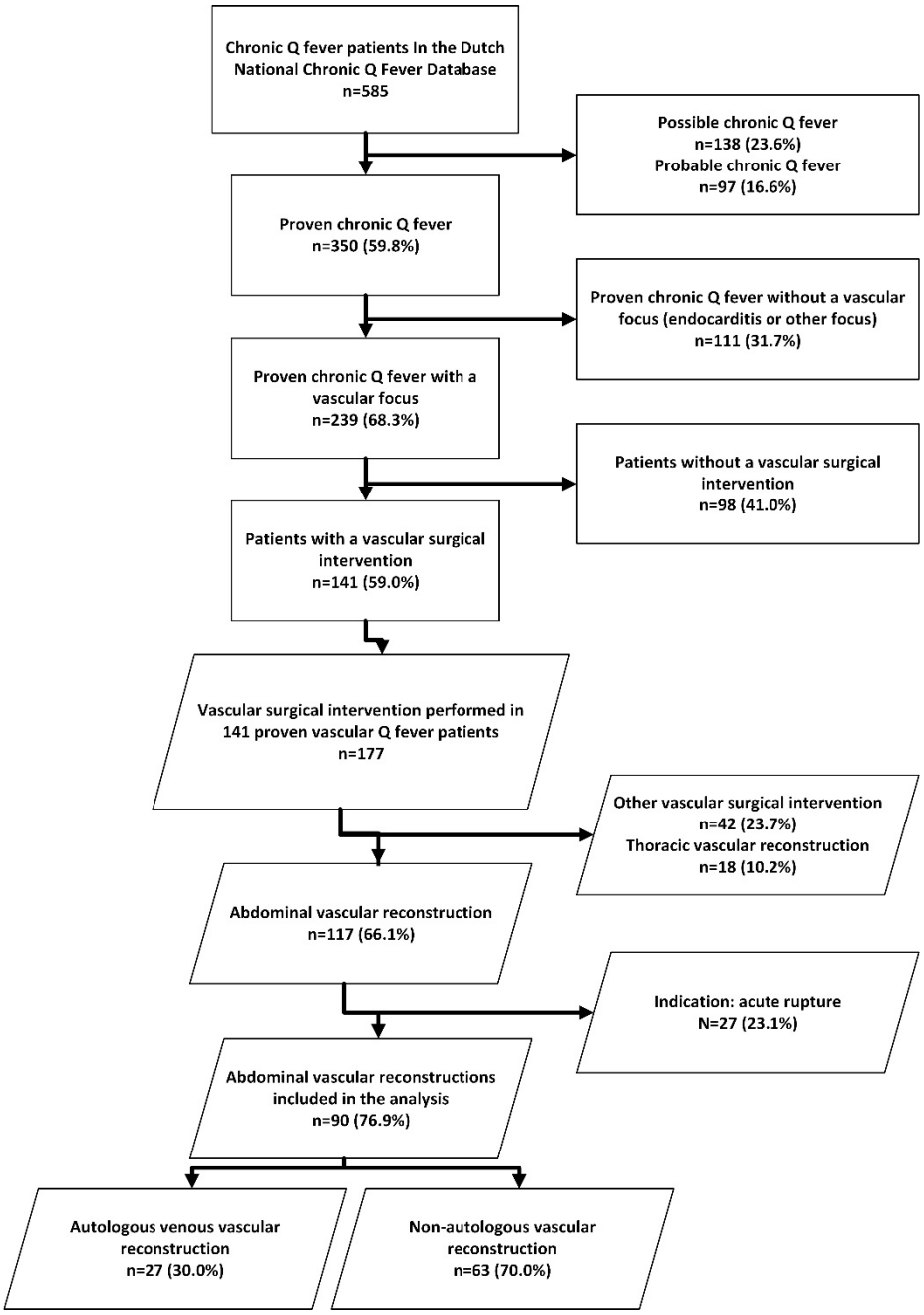

Figure 1: Flowchart of included proven vascular chronic Q fever patients (rectangles) and vascular reconstruction (parallelograms)

Table 1.

Patient and intervention characteristics of vascular reconstructions in proven vascular chronic Q fever patients

	All vascular reconstructions (n=90)	Autologous venous reconstructions (n=27)	Non-autologous reconstructions (n=63)
Number of patients [a]	81	27	59
Mean age at intervention (SD)	71.1 (7.9)	70.9 (7.0)	71.2 (7.9)
Male sex (%)	84 (93.3%)	26 (96.3%)	58 (92.1%)
Preoperative comorbidity			
Chronic kidney failure (%)	12 (13.3%)	2 (7.4%)	10 (15.9%)
Diabetes mellitus (%)	12 (13.3%)	4 (14.8%)	8 (12.7%)
Immunocompromised state (%) [b]	12 (13.3%)	3 (11.1%)	9 (14.3%)
Ischemic cardiac disease (%)	31 (34.4%)	9 (33.3%)	22 (34.9%)
Obstructive lung disease (%)	14 (15.6%)	2 (7.4%)	12 (19.0%)
Chronic Q fever characteristics			
Months between chronic Q fever diagnosis and vascular reconstruction (median, IQR)	0 (0-10)	6 (0-16)	0 (0 - 5)
Both vascular and endocarditis focus (%)	12 (13.3%)	1 (3.7%)	11 (17.5%)
Positive PCR on *C. burnetii* any time before intervention			
Positive/performed on serum (%)	45/81 (55.6%)	13/27 (48.1%)	32/54 (59.3%)
Positive/performed on tissue (%)	55/62 (88.7%)	21/25 (84.0%)	34/37 (91.9%)
Positive PCR on *C. burnetii* in 3 months before or during intervention (%)			
Positive/performed on serum (%)	27/81 (30.3%)	7/27 (25.9%)	20/54 (37.0%)
Positive/performed on tissue (%)	47/55 (85.5%)	18/23 (78.3%)	29/32 (90.6%)
Highest *C. burnetii* phase 1 IgG before intervention (median, IQR)[b]	8,192 (2,048-16,384)	8,192 (2,048-16,384)	4,096 (2,048-16,384)
Last *C. burnetii* phase 1 IgG before intervention (median, IQR) [b]	2,048 (1,024-8,192)	2,048 (1,024-8,192)	2,048 (1,024-8,192)
Antibiotic treatment during intervention (%)	48 (53.3%)	21 (77.8%)	27 (42.9%)
Intervention characteristics			
Autologous reconstruction			
Femoral vein reconstruction (%)	12 (13.3%)	12 (44.4%)	NA
Spiral vein (GSV) reconstruction (%)	15 (16.7%)	15 (55.6%)	NA
Non-autologous reconstruction			
EVAR (%)	24 (26.7%)	NA	26 (41.3%)
In situ open vascular reconstruction (%)	32 (35.6%)	NA	30 (47.6%)
Extra-anatomic bypass	7 (7.8%)	NA	7 (11.1%)
Native aneurysm repair (%)	62 (68.9%)	13 (48.1%)	49 (77.8%)
Graft repair or replacement (%)	28 (31.1%)	14 (51.9%)	14 (22.2%)
Elective intervention (%)	51 (56.7%)	21 (77.8%)	30 (47.6%)
Locations of intervention			
Abdominal aorta (%)	59 (65.6%)	17 (63.0%)	42 (66.7%)
Iliac artery (%)	5 (5.6%)	1 (3.7%)	4 (6.3%)
Both abdominal aorta and iliac artery (%)	26 (28.9%)	9 (33.3%)	17 (27.0%)
Indication of intervention			
Aneurysm or vascular graft without known signs of infection	30 (33.3%)	3 (11.1%)	27 (42.9%)
Infected aneurysm or vascular graft	22 (24.4%)	5 (18.5%)	17 (27.0%)

without abscess or fistula			
Infected aneurysm or vascular graft with abscess or fistula	38 (42.2%)	19 (70.4%)	19 (30.2%)

Abbreviations: SD, standard deviation; IQR, interquartile range; EVAR, endovascular aneurysm repair; GSV, greater saphenous vein; NA, not applicable

[a] Three patients had a second non-autologous vascular reconstruction, four patients also had an autologous venous reconstruction after their first non-autologous vascular reconstruction and one patient had two non-autologous vascular repairs before a autologous venous vascular reconstruction

[b] Immunocompromised was defined as the use of corticosteroids (prednisone or equivalent, cumulative dose > 700 mg), anti-CD20 therapy, biologicals (TNF-alpha inhibitors, interleukin-5 inhibitors and monoclonal antibodies), methotrexate, azathioprine and/or mercaptopurine within the last 6 months, having received an autologous/allogenic stem-cell transplantation, having neutropenia (< 0.5 × 109/L), (functional) hypo/asplenia, CD4-penia (< 200 cells/mm3), hypogammaglobinemia and/or having another primary immunodeficiency

[c] *C. burnetii* phase I IgG titers were missing in four abdominal vascular reconstructions.

Table 2

Overview of clinical outcomes after abdominal and iliac vascular reconstructions in proven vascular chronic Q fever patients

	All vascular reconstructions (n=90)	Autologous venous reconstructions (n=27)	Non-autologous reconstructions (n=63)
Follow-up time in months (Median, IQR)	37.5 (9.8 – 69.0)	31.0 (14.0 - 65.0)	41.0 (7.0 - 69.0)
All-cause mortality (%)	43 (47.8%)	11 (40.7%)	32 (50.8%)
30-day mortality (%)	8 (8.9%)	3 (11.1%)	5 (7.9%)
Vascular chronic Q fever-related mortality (%)	28 (31.1%)	5 (18.5%)	23 (36.5%)
Complication of aneurysm (%)	10 (11.1%)	0 (-)	10 (15.9%)
Surgical complications (%)	10 (11.1%)	3 (11.1%)	7 (11.1%)
Clinical deterioration (%)	6 (6.7%)	2 (7.4%)	4 (6.3%)
Side effects of antibiotic therapy (%)	1 (1.11%)	0 (-)	1 (1.6%)
Unknown (%)	1 (1.11%)	0 (-)	1 (1.6%)
Vascular chronic Q fever-related complications (%)	25 (27.8%)	3 (11.1%)	22 (34.9%)
Total number of complications	34	3	31
Ruptured aneurysm (%)	2 (5.9%)	0 (-)	2 (6.5%)
Endoleak prosthesis (%)	7 (20.6%)	0 (-)	7 (22.6%)
Fistula (%)	6 (17.6%)	0 (-)	6 (19.4%)
Abscess (%)	9 (26.5%)	0 (-)	9 (29.0%)
Arterial embolic complications (%)	1 (2.9%)	0 (-)	1 (3.2%)
Significant graft stenosis or occlusion (%)	4 (11.8%)	1 (33.3%)	3 (9.7%)
Symptomatic aneurysm, without other complication	3 (8.8%)	1 (33.3%)	2 (6.5%)
Other (%)	2 (5.9%)	1 (33.3%)[a]	1 (3.2%)[b]
Q fever-related (re)interventions after initial surgery (%)	20 (22.2%)	1 (3.7%)	19 (30.2%)
Total number of (re)interventions after initial surgery	24	2	22
Graft repair or replacement (%)	8 (33.3%)	2 (100%)	6 (27.3%)
Venous reconstruction (%)	5 (20.8%)	0 (-)	5 (22.7%)
Debridement/drainage(%)	7 (29.2%)	0 (-)	7 (31.8%)
Coiling/embolization (%)	3 (12.5%)	0 (-)	3 (13.6%)
Surgical intervention withheld due to bad condition patient (%)	1 (6.3%)	0 (-)	1 (4.5%)
Positive *C. burnetii* PCR after 3 months negative PCR or persistent positive PCR after 6 months therapy (%)	12 (13.3%)	2 (7.4%)	10 (15.9%)

Abbreviations: IQR, interquartile range; PCR, polymerase chain reaction;

[a] Abdominal compartment syndrome after vascular reconstruction

[b] Chylous leakage after vascular reconstruction

Table 3a

Risk of early (Q fever-related) mortality and Q fever-related events in the first 3 months after abdominal vascular reconstructions

Outcomes measures	Autologous venous reconstructions (n=27)	Non-autologous reconstruction (n=63)	Adjusted HR (CI)[a,b]
All-cause mortality (%)	4 (14.8%)	9 (14.3%)	1.82 (0.39 - 7.84)
Q fever-related mortality (%)	4 (14.8%)	9 (14.3%)	1.82 (0.39 - 7.84)
Q fever-related event (%)	5 (18.5%)	11 (17.5%)	1.46 (0.33 - 5.83)

Table 3b

Risk of late (Q fever-related) mortality, Q fever-related events, and Q fever therapy failure from 3 months after abdominal vascular reconstructions with a median follow-up of 37.5 months

Outcome measures	Autologous venous reconstructions (n=22)	Non-autologous reconstruction (n=52)	Adjusted HR (CI)[a,b]	Adjusted SHR (CI)[a,b]
All-cause mortality (%)	7 (31.8%)	22 (42.3%)	0.67 (0.22 - 2.06)	0.68 (0.24 - 1.95)
Q fever-related mortality (%)	1 (4.5%)	13 (25.0%)	0.14 (0.01 - 1.47)	0.11 (0.01 - 1.23)
Q fever-related event (%)	2 (9.1%)	30 (57.7%)	0.08 (0.02 - 0.43)	0.08 (0.02 - 0.37)
Q fever therapy failure (%)	4 (18.2%)	32 (61.5%)	0.12 (0.03 - 0.44)	0.11 (0.03 - 0.39)

Abbreviations: HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio;

[a] Corrected for age at intervention, comorbidities, positive *C. burnetii* PCR on serum/blood at any time before intervention, elective or emergency surgery, a native aneurysm repair or prostheses replacement, and if the intervention took place at Intervention took place at Q fever diagnosis or more than 1 month after

[b] Stratified by the indication of intervention (symptomatic aneurysm without abscess or fistula, growth or large diameter of asymptomatic aneurysm, infective aneurysm with abscess or fistula, or endoleak of current prosthesis)

Supplementary text

Complication and cause of death potentially related to vascular chronic Q fever (definition in the Dutch National Chronic Q Fever Database)(2,7,18,24,25)

Complications considered potentially related to chronic Q fever were rupture of the aneurysm or dissection of the aneurysm; arterial fistula (arterio-bronchial, arterio-cutaneous, arterio-caval or arteriodigestive fistula); endoleak of vascular prostheses; vertebral osteomyelitis; osteomyelitis (other than spondylitis); abscess (psoas region, intra-abdominal, retroperitoneal, intrathoracic, other); acute symptomatic aneurysm (without simultaneous intra-abdominal or retroperitoneal abscess/vertebral osteomyelitis/rupture of aneurysm/dissection of aneurysm/fistula).

Cause of death was defined as definitely or probably related to chronic Q fever in case of active disease and cause of death potentially related to chronic Q fever. Active disease was defined as phase I IgG≥1,024 or positive PCR on serum or tissue. Causes of death potentially related to chronic Q fever were sepsis/feverish episode with no other cause; arterial fistula; ruptured or dissected aneurysm; complications after vascular surgery; side effects of antibiotic therapy; clinical deterioration during active disease with no other cause; Q fever as cause of death proven by autopsy; unknown cause in the presence of Q fever-related complications; or unknown cause without adequate Q fever treatment.

Supplementary table 1.

Diagnostic criteria for chronic Q fever formulated by the Dutch Q Fever Consensus Group [2]

Proven chronic Q fever	Probable chronic Q fever	Possible chronic Q fever
1. Positive *C. burnetii* PCR in blood or tissue [a] OR 2. IFA ≥1:1024 for *C. burnetii* phase I IgG AND - definite endocarditis according to modified Duke criteria [19] OR - proven large vessel or prosthetic infection by imaging studies (^{18}F-FDG-PET, CT, MRI or AUS)	1. IFA ≥1:1024 for *C. burnetii* phase I IgG AND one or more of the following criteria: - valvulopathy not meeting the major criteria of the modified Duke criteria (26) - known aneurysm and/or vascular or cardiac valve prosthesis without signs of infection by means of TEE/TTE, ^{18}F-FDG-PET, CT, MRI or AUS - suspected osteomyelitis or hepatitis as manifestation of chronic Q fever - pregnancy - symptoms and signs of chronic infection, such as fever, weight loss and night sweats, hepato-splenomegaly, persistent raised ESR and CRP - granulomatous tissue inflammation, proven by histological examination - immunocompromised state	1. IFA ≥1:1024 for *C. burnetii* phase I IgG without manifestations meeting the criteria for proven or probable chronic Q fever

Abbreviations: PCR, polymerase chain reaction; IFA, immunofluorescence assay; FDG-PET, fludeoxyglucose positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; AUS, abdominal ultrasound; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

[a] In absence of acute infection

Supplementary table 2

Risk of late (Q fever-related) mortality, Q fever-related events, and Q fever therapy failure from 3 months after abdominal vascular reconstructions (Sensitivity analyses excluding second and third intervention in the same patients)

Outcomes measures	Autologous venous reconstructions (n=18)	Non-autologous vascular reconstruction (n=49)	Adjusted HR (CI)[a,b]	Adjusted SHR (CI) [a,b]
All-cause mortality (%)	5 (27.8%)	22 (44.9%)	0.58 (0.17 - 2.00)	0.58 (0.17 - 1.91)
Q fever-related mortality (%)	1 (4.5%)	13 (26.5%)	0.12 (0.01 - 1.51)	0.10 (0.01 - 1.53)
Q fever-related event (%)	2 (11.1%)	28 (57.1%)	0.12 (0.02 - 0.63)	0.10 (0.02 - 0.52)
Q fever therapy failure (%)	4 (22.2%)	30 (61.2%)	0.16 (0.04 - 0.60)	0.14 (0.04 - 0.52)

[a] Corrected for age at intervention, comorbidities, positive C. burnetii PCR on serum/blood at any time before intervention, elective or emergency surgery, a native aneurysm repair or prostheses replacement, and a dichotomous variable if the intervention took place before or at diagnosis of chronic Q fever, or more than 1 month after diagnosis

[b] Stratified by the indication of intervention (symptomatic aneurysm without abscess or fistula, growth or large diameter of asymptomatic aneurysm, infective aneurysm with abscess or fistula, or endoleak of current prosthesis)

Supplementary table 3

Risk of late (Q fever-related) mortality, Q fever-related events, and Q fever therapy failure from 3 months after abdominal vascular reconstructions (subgroup analyses excluding extra-anatomic bypasses)

Outcomes measures	Autologous venous reconstructions (n=22)	Non-autologous vascular reconstruction (n=46)	Adjusted HR (CI)[a,b]	Adjusted SHR (CI) [a,b]
All-cause mortality (%)	7 (31.8%)	19 (41.3%)	0.63 (0.19 – 2.17)	0.63 (0.19 – 2.03)
Q fever-related mortality (%)	1 (4.5%)	12 (26.1%)	0.04 (0.00 – 0.79)	0.05 (0.01 – 0.47)
Q fever-related event (%)	2 (9.1%)	26 (56.5%)	0.07 (0.01 – 0.40)	0.07 (0.02 – 0.30)
Q fever therapy failure (%)	4 (18.2%)	28 (60.9%)	0.09 (0.02 – 0.34)	0.09 (0.03 – 0.31)

[a] Corrected for age at intervention, comorbidities, positive C. burnetii PCR on serum/blood at any time before intervention, elective or emergency surgery, a native aneurysm repair or prostheses replacement, and a dichotomous variable if the intervention took place before or at diagnosis of chronic Q fever, or more than 1 month after diagnosis

[b] Stratified by the indication of intervention (symptomatic aneurysm without abscess or fistula, growth or large diameter of asymptomatic aneurysm, infective aneurysm with abscess or fistula, or endoleak of current prosthesis)