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Association Between Vegetation Size and Outcome in the Partial Oral Antibiotic Endocarditis Treatment Trial

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Step-down oral antibiotic therapy is associated with a non-inferior long-term outcome compared with continued intravenous antibiotic therapy in the treatment of left-sided infective endocarditis. We aimed to analyze whether step-down oral therapy compared with continued intravenous antibiotic therapy is also associated with a non-inferior outcome in patients with large vegetations (vegetation length ≥ 10 mm) or among patients who underwent surgery before step-down oral therapy. We included patients without presence of aortic root abscess at diagnosis from the POET (Partial Oral Antibiotic Endocarditis Treatment) study. Multivariable Cox regression analyses were used to find associations between large vegetation, cardiac surgery, step-down oral therapy, and the primary end point (composite of all-cause mortality, unplanned cardiac surgery, embolic event, or relapse of positive blood cultures during follow-up). A total of 368 patients (age 68 ± 12, 77% men) were included. Patients with large vegetations (n = 124) were more likely to undergo surgery compared with patients with small vegetations (n = 244) (65% vs 20%, p <0.001). During a median 1,406 days of follow-up, 146 patients reached the primary end point. Large vegetations were not associated with the primary end point (hazard ratio 0.74, 95% confidence interval 0.47 to 1.18, p = 0.21). Step-down oral therapy was non-inferior to continued intravenous antibiotic in all subgroups when stratified by the presence of a large vegetation at baseline and early cardiac surgery. Step-down oral therapy is safe in the presence of a large vegetation at diagnosis and among patients who underwent early cardiac surgery. **(Am J Cardiol 2024;222:131−140)**

Keywords: cardiac surgery, infective endocarditis, stroke, transesophageal echocardiography

Infective endocarditis (IE) is a severe disease, with reported in-hospital mortality around 20% and a high rate of in-hospital morbidity.[1−3] For patients surviving the initial admission, long-term mortality is increased compared with the background population.[4,5] IE patients are generally becoming older at the time of diagnosis and have more comorbidities,[3,6] and some studies report an increasing incidence over time.[3,7]

The POET trial (Partial Oral Antibiotic Endocarditis Treatment) was a randomized clinical trial where step-

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See page 138 for Declaration of Competing Interest.

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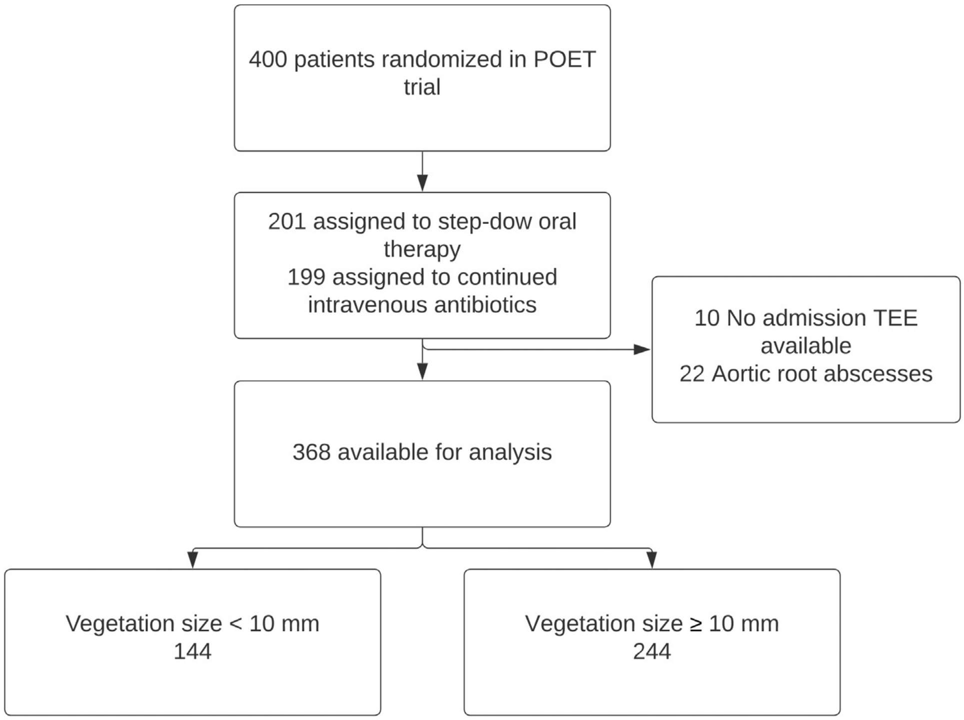

Figure 1. CONSORT diagram. CONSORT diagram of the inclusion of patients in the present sub study. CONSORT = Consolidated Standards of Reporting Trials.

down oral antibiotic therapy was initiated after an initial stabilization with intravenous antibiotics. Step-down oral therapy was found to be non-inferior to continued intravenous infusion.[8] Based on this trial, step-down oral therapy has now been included in the most recent European IE guidelines as a class 2A recommendation in stable IE patients.[9] Since a large vegetation ≥ 10 mm at diagnosis in some studies has been associated with an adverse outcome,[10−13] uncertainty may arise as to whether these patients may qualify for step-down oral therapy. Further, it is unknown whether step-down oral therapy is safe in patients who have undergone cardiac surgery during the initial hospitalization.

The aims of this study were therefore to examine the association between a large vegetation at the diagnostic transesophageal echocardiogram (TEE) and outcome in the POET trial and to examine whether step-down oral therapy was safe among patients in the POET trial with a large vegetation at diagnosis and among patients who had undergone cardiac surgery before randomization.

Methods

The POET trial was an investigator-driven, multicenter, randomized, non-inferiority trial performed in Denmark between 2011 and 2017. Detailed descriptions of the study protocol have been published previously.[8,14]

Eligible patients were ≥18 years of age, in treatment for left-sided definite IE, and in stable condition after at least 10 days of adequate intravenous antibiotic treatment for IE. Further, patients were required to have positive blood cultures for *Streptococcus spp, Enterococcus faecalis, Staphylococcus aureus*, or coagulase-negative *Staphylococci*. A diagnostic TEE was performed on all patients. At the time of randomization, a repeat TEE was required to rule out new abscess formation or severe valvular complications requiring surgery (the repeat TEE was not part of this study). Patients who had undergone immediate cardiac surgery were required to take at least 7 days of intravenous antibiotics before randomization. Cardiac surgery and pacemaker extractions were performed after a multidisciplinary team decision and were not part of the study protocol.

In the present study, we excluded patients without an available diagnostic TEE and patients with visible aortic root abscess (defined as a thickened area or mass with a heterogeneous echogenic or echo lucent appearance) on the diagnostic TEE (Figure 1).

All diagnostic TEEs were analyzed retrospectively by a single experienced cardiologist (RC-S), blinded to all variables but age and gender, using IntelliSpace Cardiovascular 4.2 (Philips Medical Systems, PC Best, The Netherlands) or ViewPoint 6.11 (GE Healthcare GmbH, Solingen, Germany). In cases of unclear or ambiguous findings, a second experienced cardiologist (NI) was consulted.

The length of the vegetation was measured. Mobility was graded as none/minimal, moderate, or severe as described by Thuny et al.[15] The shape of the vegetation was further described modified from Pérez-García et al[16] as filiform (major-to-minor diameter > 2), solid and homogenously shaped, solid and lobulated/heterogeneous, thickened valve, or other (e.g., aneurysmatic valve) (Figure 2). In cases where more than one vegetation was present, the largest was measured and described.

Valvular regurgitation and stenosis were described as recommended by the European Society of Echocardiography.[17−19] The presence of the following was recorded:

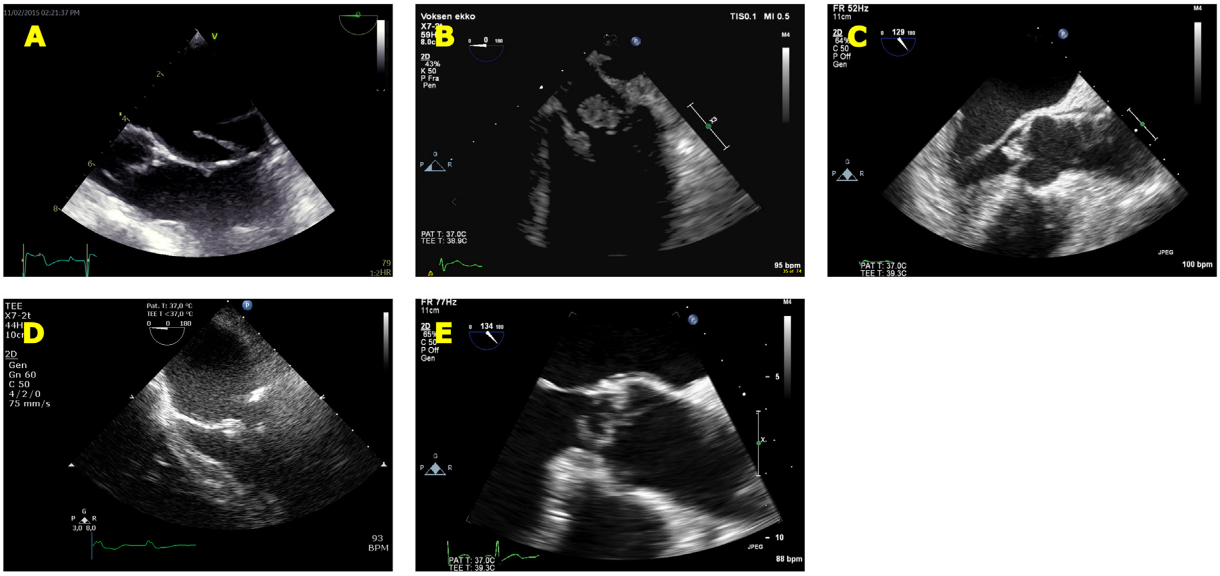

Figure 2. Morphological vegetation variants. Morphological types of vegetations: (*A*) filiform/tubular, (*B*) solid and homogenous, (*C*) solid and inhomogenous/lobulated, (*D*) thickened valve, and (*E*) other (here aneurysmatic aortic valve).

Fistulae, defined as abnormal flow between chambers; Barlow's mitral valve disease, defined as a bileaflet prolapse with excessive and thickened leaflet tissue; mitral valve prolapse; a bicuspid aortic valve; and a persistent foramen ovale or atrial septal defect.

TTEs at diagnosis were analyzed when available for left ventricular ejection fraction tricuspid annular plane systolic excursion according to guidelines.[20]

According to the diagnostic TEE, patients were divided into 2 groups: (1) small vegetation (<10 mm in length) or (2) large vegetation (≥10 mm length).

Patients were followed through chart review, and no patients were lost to follow-up.[21] The primary end point was defined as a composite of all-cause mortality, IE-related cardiac surgery after randomization, embolic event, or relapse of positive blood cultures during follow-up.[8]

Data are presented as mean ± SD, median and (interquartile range) or number (percentages) as appropriate. Normality of data was tested visually by qq-plots and histograms. Normally distributed variables were tested with Student's *t* test, nonparametric variables were tested by Wilcoxon signed-rank test, and categorical variables were tested by the chi-square test unless the number of events was lower than 5, in which case the Fischer's exact test was used.

Multivariable logistic regression analyses of the association between length of the vegetation at diagnosis and surgery before randomization was performed, adjusting for age, gender, diabetes, nephropathy, chronic obstructive pulmonary disease, and liver disease.

A multivariable Cox regression analysis was performed to assess the association between large vegetation size and the primary end point, adjusting for previously found variables associated with the end point in POET trial[22] (age, diabetes, renal failure, prosthetic aortic valve, IE-related heart surgery before randomization, and step-down oral therapy) and gender.

To test if step-down oral therapy was associated with the primary end point in different subgroups, we performed univariable Cox regression interaction analyses between step-down oral therapy and large vegetation size for patients with and without surgery before randomization. Afterwards, Kaplan-Meier curves and univariable Cox regression analysis were performed to compare the primary end point stratified by treatment arm (step-down oral therapy/intravenous) and whether patients had undergone surgery before randomization within the small and large vegetation groups.

STATA/BE 18.0 (StataCorp LLC, College Station, TX) software was used.

Results

After exclusion of patients without an available diagnostic TEE (n = 10) and patients with an aortic root abscess (n = 22), 368 patients were included in the study (age 68 ± 12, 283 (77%) men) (Figure 1). Using a vegetation length cutoff of 10 mm, 124 (34%) were in the large vegetation group (66 ± 11 years, 76% men), and 244 (66%) were in the small vegetation group (69 ± 12 years, 77% men). The small vegetation patients were older and more likely to have diabetes. They had a shorter duration from diagnosis to randomization, and at randomization, they had lower C-reactive protein and leukocyte count and higher hemoglobin. Small vegetations were more often associated with *S aureus*, and large vegetations with *streptococcus spp* (Table 1).

Echocardiographic data are presented in Table 2, and the size of aortic and mitral vegetations is shown in Figure 3. The large vegetation group more often had vegetations located to the mitral valve. In addition to being larger, the large vegetations were more mobile. The large vegetations were often filiform or lobulated, while the small vegetations were more homogenously shaped (Table 2).

Table 1
Baseline demographics, co-morbidities, bacterial agents, and biomarkers according to vegetation size

	Vegetation < 10 mm	Vegetation ≥ 10 mm	P-value
Number of patients	244	124	
Demographics and co-morbidities			
Age (years)	69±12	66±11	0.03
Sex (male)	189 (77)	94 (76)	0.72
Pacemaker/ICD	28 (11)	7 (6)	0.07
Nephropathy	32 (13)	13 (10)	0.47
Dialysis	21 (9)	7 (6)	0.31
Liver disease	10 (4)	2 (2)	0.2
Diabetes mellitus	56 (23)	11 (9)	0.001
Chronic obstructive pulmonary disease	20 (8)	7 (6)	0.38
Intravenous substance use disorder	3 (1)	2 (2)	0.74
Cancer (active or in remission)	20 (8)	12 (10)	0.64
Bacterial agent			
Streptococcus spp	86 (44)	27 (61)	0.004
Enterococcus faecalis	50 (26)	10 (23)	0.45
Staphylococcus aureus	54 (28)	6 (14)	0.002
Coagulase-negative staphylococci	6 (3)	2 (5)	0.43
Treatment			
Step-down oral antibiotics	95 (48)	26 (59)	0.83
Time from diagnosis to randomization	16 [12-22]	18 [13-24]	0.03
Time from randomization to ended treatment	19 [15-26]	16 [14-24]	0.002
Biomarkers at time of randomization			
Temperature (˚C)	36.9±0.4	37.0±0.5	0.002
Leucocytes (10^9/L)	6.9 [5.4-8.5]	7.4 [6.1-8.8]	0.54
CRP (mg/L)	15 [7-27]	22 [13-34]	0.0007
Hemoglobin (mmol/L)	6.5 [5.7-7.4]	6.0 [5.4-6.7]	0.0001
Creatinine (micromol/L)	93 [74-120]	86 [70-103]	0.32

Numbers indicate mean±SD, numbers (percentages), or median [Q1-Q3] as appropriate.
COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ICD = implantable cardioverter-defibrillator.

Aortic vegetations ≥10 mm (n = 52) were more often associated with ≥moderate aortic regurgitation compared with patients with aortic vegetations <10 mm (n = 158) and patients without aortic vegetations (n = 158) (respectively, 79%, 33%, and 10%, p <0.001) (Figure 4, upper panel). Similarly, mitral vegetations ≥10 mm (n = 75) were more often associated with ≥ moderate mitral regurgitation compared with patients with mitral vegetations <10 mm (n = 85) and patients without mitral vegetations (n = 208) (respectively, 76%, 47%, and 10%, p <0.001) (Figure 4, lower panel). A perforated valve was more common in the large vegetation group compared with the small vegetation group (57% vs 19%, p <0.001).

A total of 147 patients (38%) underwent surgery before randomization, with a significantly higher rate in the large vegetation group compared with the small vegetation group (65% vs 20%, p <0.001).

In Supplementary Tables 1 and 2, baseline and imaging data are presented for large vegetation and small vegetation groups stratified by surgery before randomization. For both groups, patients who underwent surgery were younger and less likely to have chronic kidney disease. For surgically managed patients, there was a longer timespan from diagnosis to randomization but a shorter timespan from randomization to end of antibiotic treatment. At randomization, surgically managed patients had higher C-reactive protein and lower hemoglobin values. There were no differences in rates of step-down oral therapy between groups.

With multivariable logistic regression analysis as described above, large vegetations were associated with a significantly higher risk of surgery before randomization (adjusted odds ratio 7.86, 95% confidence interval [CI] 4.57 to 13.49, p <0.001) (Supplementary Table 3).

In total, 37 patients (10%) had a stroke before randomization. This rate was higher in the large vegetation group compared with the small vegetation group (15 vs 8%, p = 0.04). Due to the limited number of events and because we did not have data on whether these strokes occurred before or after any cardiac surgery, we chose not to perform a multivariate analysis on the association between large vegetation size and stroke.

During a median follow-up period of 1,406 (interquartile range 933 to 2,127) days, 146 patients (40%) reached the primary end point. Of these, 110 died, 32 had IE-related surgery, 18 had a relapse of positive blood cultures, and 12 had an embolic event. Large vegetations were not associated with the primary end point in multivariable Cox regression analysis (hazard ratio 0.74, 95% CI 0.47 to 1.18, p = 0.21).

Overall, there was no interaction between surgery before randomization and step-down oral treatment (p for interaction = 0.32). Among patients without surgery before randomization, we found a significant interaction between large vegetation size and stand-down oral therapy (p for interaction = 0.03). There was no corresponding interaction among patients with surgery before randomization (p for interaction = 0.59).

Table 2
Baseline imaging data according to vegetation size

	Vegetation < 10 mm	Vegetation ≥ 10 mm	P-value
Number of patients	244	124	
Right and left ventricular function			
LV ejection fraction (%)	55±10	57±10	0.15
TAPSE (mm)	23±8	25±7	0.14
Valve involved			
Aortic valve	155 (64)	65 (52)	0.04
Mitral valve	81 (33)	81 (65)	<0.001
Tricuspid valve	5 (2)	2 (2)	0.77
Pacemaker vegetation	12 (5)	2 (2)	0.12
Type of valve			
Native	172 (70)	105 (85)	0.003
Biological	61 (25)	14 (11)	0.002
Mechanical	11 (5)	5 (4)	0.83
Other abnormalities			
Mitral Barlow’s valve and/or prolapse	20 (8)	13 (10)	0.47
Bicuspid aortic valve	13 (5)	5 (4)	0.59
PFO/ASD	27 (16)	15 (20)	0.48
Regurgitation			
≥Moderate aortic regurgitation	61 (65)	48 (39)	0.006
≥Moderate mitral regurgitation	54 (22)	63 (51)	<0.001
≥Moderate tricuspid regurgitation	10 (4)	11 89)	0.06
Stenosis			
≥Moderate aortic stenosis	24 (10)	4 (3)	0.02
≥Moderate mitral stenosis	6 (2)	3 (2)	1.00
Vegetation size			
Maximal length (mm)	5 [3-6]	13 [11-17]	<0.0001
Movement (1-3) (in %)	35/54/11	7/23/70	<0.001
Vegetation morphology and complication			
Filiform	89 (37)	67 (54)	0.001
Solid, homogenous	93 (38)	16 (13)	<0.001
Solid, inhomogenous	19 (8)	38 (31)	<0.001
Thickened valve	10 (4)	1 (1)	0.11
Other	5 (2)	2 (2)	1.00
Perforated valve	46 (19)	71 (57)	<0.001
Fistula	0 (0)	0 (0)	1.00

Numbers indicate mean±SD, numbers (percentages), or median [Q1-Q3] as appropriate.
ASD = atrial septal defect; LV = left ventricular; PFO = persistent foramen ovale; TAPSE = tricuspid annular plane systolic excursion.

With univariable Cox regression analysis and stratified by step-down oral therapy and cardiac surgery, step-down oral therapy was not associated with an increased risk of reaching the primary end point in either the small vegetation or large vegetation group and was even associated with a reduced risk of reaching the primary end point among patients without surgery before randomization with large vegetation (hazard ratio 0.27, 95% CI 0.10 to 0.72, p = 0.009) (Figure 5).

Discussion

In this analysis of the largest randomized clinical trial regarding endocarditis to date, we find that among patients with IE who have survived the initial hospitalization, step-down oral therapy is a safe option to treat patients who have stabilized after initial intravenous therapy, regardless of a large vegetation size at diagnosis and whether early cardiac surgery has been performed.

The length of the presenting vegetation has in several studies been associated with a poorer outcome. Larger vegetations have thus been associated with increased in-hospital mortality,[10−13] embolic events,[2,15,16,23,24] and long-term mortality.[15,24] Similar to a study from Young et al,[25] we found that large vegetations were associated with more severe valvular regurgitation at baseline. This is likely due to more longstanding and/or more virulent bacteremia with associated destruction of the affected valve and, hence, more pronounced regurgitation.

In relation to this, we found that a large vegetation was associated with increased risk of in-hospital surgery. This may in part be due to the more pronounced regurgitations and larger proportion of perforated valves associated with large vegetations in our study. However, a part of the association may be rooted in the guidelines, where vegetations >30 mm or vegetations >10 mm accompanied by embolic episodes constitute indications for surgery.[9]

Lastly, we found that the number of patients with a stroke before randomization was higher in the large vegetation group. Due to a limited number of strokes before randomization, and because we did not have data on whether these strokes occurred before or after surgery, we did not

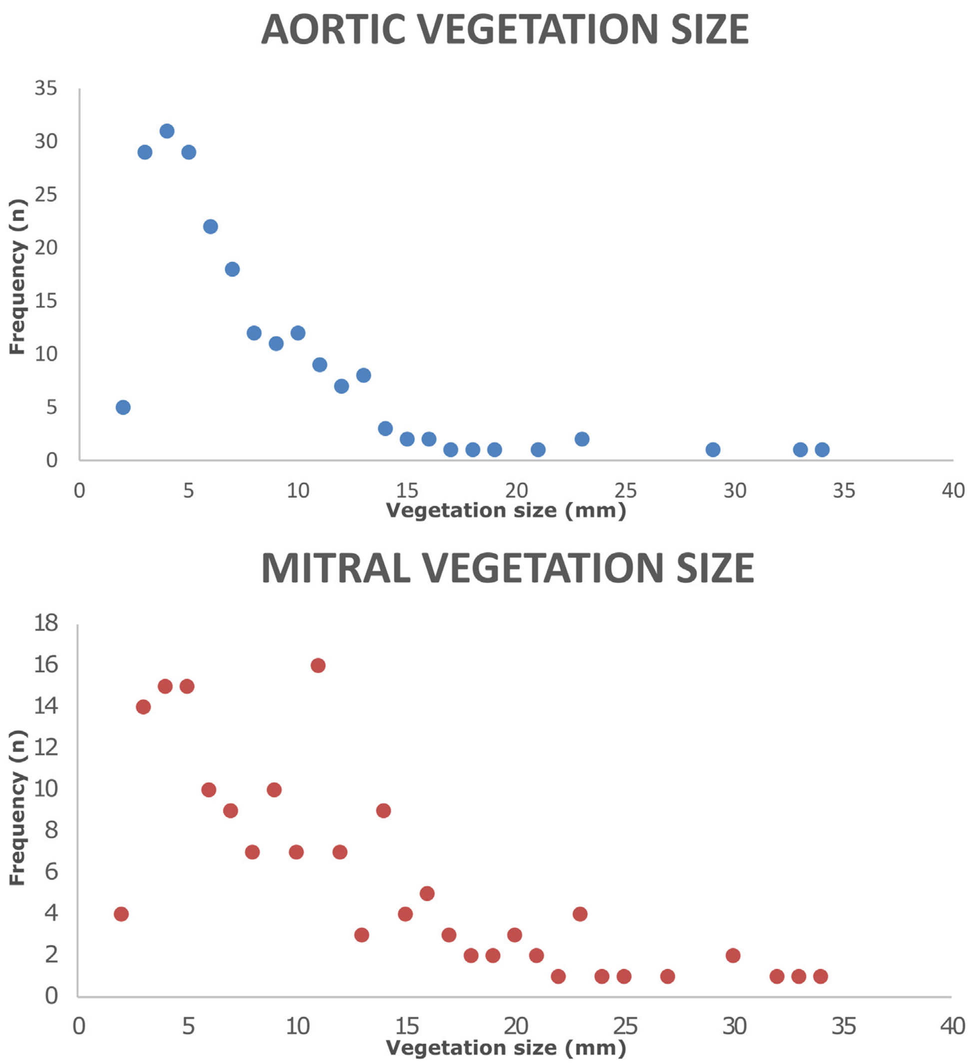

Figure 3. Vegetation size Frequency of different aortic (*upper panel*) and mitral (*lower panel*) vegetation lengths.

perform any in-depth analyses on this association. However, it is in concordance with the findings of others, namely that a large vegetation is associated with an increased risk of stroke.[23]

Our study thus confirms that a vegetation ≥10 mm is a serious finding, associated with a high risk of in-hospital complications. Whether these patients should undergo surgery up-front or be medically managed initially is still a topic of debate that cannot be answered in observational trials but should be eventually tested in a randomized trial.[24]

In contrast, we did not find any association between the size of the vegetation at baseline and the primary end point. A large part of the reason for this finding is the setup of the study. In contrast to other studies, patients were only allowed to enter the study if they were stable on intravenous antibiotics at the time of the randomization. Many complications of endocarditis, including stroke, occur in the period immediately around diagnosis.[26] Complications such as septic shock and severe embolic events have a severe impact on long-term outcome,[1,27,28] and many of these patients and patients with early mortality were by design excluded from our cohort. Further, a large proportion of patients with large vegetation had undergone and survived surgery and were in stable condition. In our study and in several other studies, surgery is associated with a better long-term outcome, in part because of a selection bias where the more co-morbid and frail patients are not offered surgery.[1,24,27–29]

Interestingly, we found that patients with step-down oral therapy were associated with a non-inferior outcome regardless of vegetation size and cardiac surgery before step-down oral therapy. The most interesting group was the large vegetation group without cardiac surgery before step-down oral therapy. These patients would be expected to have a large bacterial load, and therefore they might be at risk of developing valvular complications or septic emboli if not treated with a full regimen of intravenous antibiotics. One might therefore speculate that they would not be optimal candidates for step-down oral therapy. However, among medically managed patients with large vegetations, step-down oral therapy was even associated with a better long-term outcome compared with continued intravenous antibiotic therapy. Although this finding was statistically highly significant, the results should be interpreted with

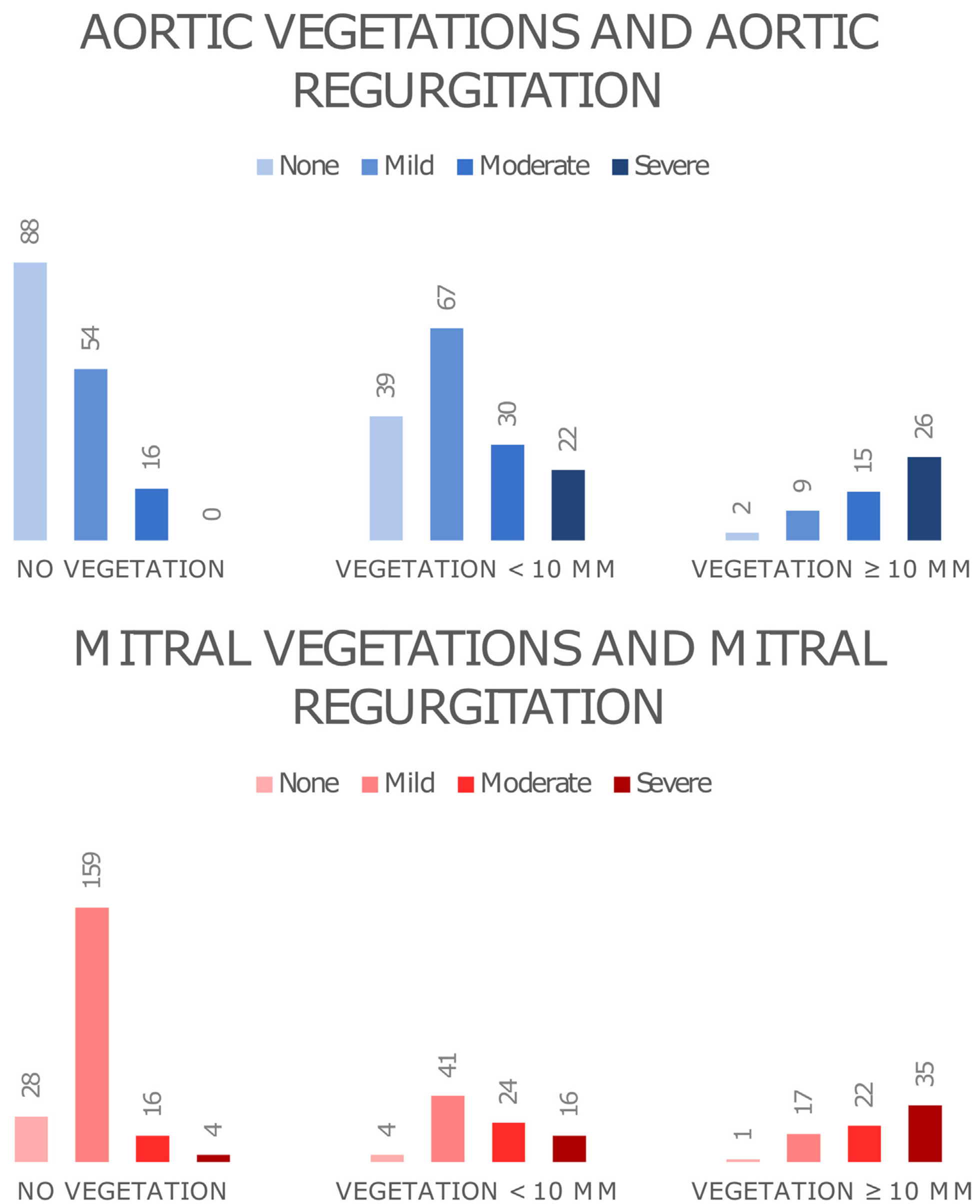

Figure 4. Vegetation size and degree of valvular regurgitation *Upper panel*: aortic vegetation size and degree of aortic regurgitations; *lower panel*: mitral vegetation size and degree of mitral regurgitations

caution, as patients by study design were not stratified by vegetation size and because the number of patients in this subgroup was low. However, we can conclude that step-down oral therapy does not appear to be associated with a poorer long-term prognosis in stable patients who have survived the initial hospitalization, regardless of vegetation size and early cardiac surgery. This illustrates that the oral antibiotic strategies in the POET trial were sufficient to maintain infectious control even in the patients with the largest vegetations.[8] Why step-down oral therapy could be associated with a positive long-term outcome in the POET trial is debatable, but previous studies have shown the detrimental effects of longer hospital stays, especially in the older people.[30]

Our study involves the largest randomized study regarding endocarditis to date. Further, TEEs were of good quality and were systematically and meticulously analyzed by a single experienced cardiologist. However, as previously described, this was a selected cohort, as the more unstable endocarditis patients were excluded from this study. Our data cannot therefore be extended to patients not fulfilling the POET study criteria. It also included only certain bacterial species; although these constitute the vast majority of microbial etiologies of IE, care should be taken before extending our findings to other and more rare bacterial species or culture-negative IE. Finally, we excluded aortic root abscesses at diagnosis from this study, so our findings cannot be extended to these patients.

Among stable IE patients with a large vegetation at diagnosis, step-down oral therapy is not associated with a negative long-term outcome. A large vegetation at baseline or early cardiac surgery should therefore not be considered

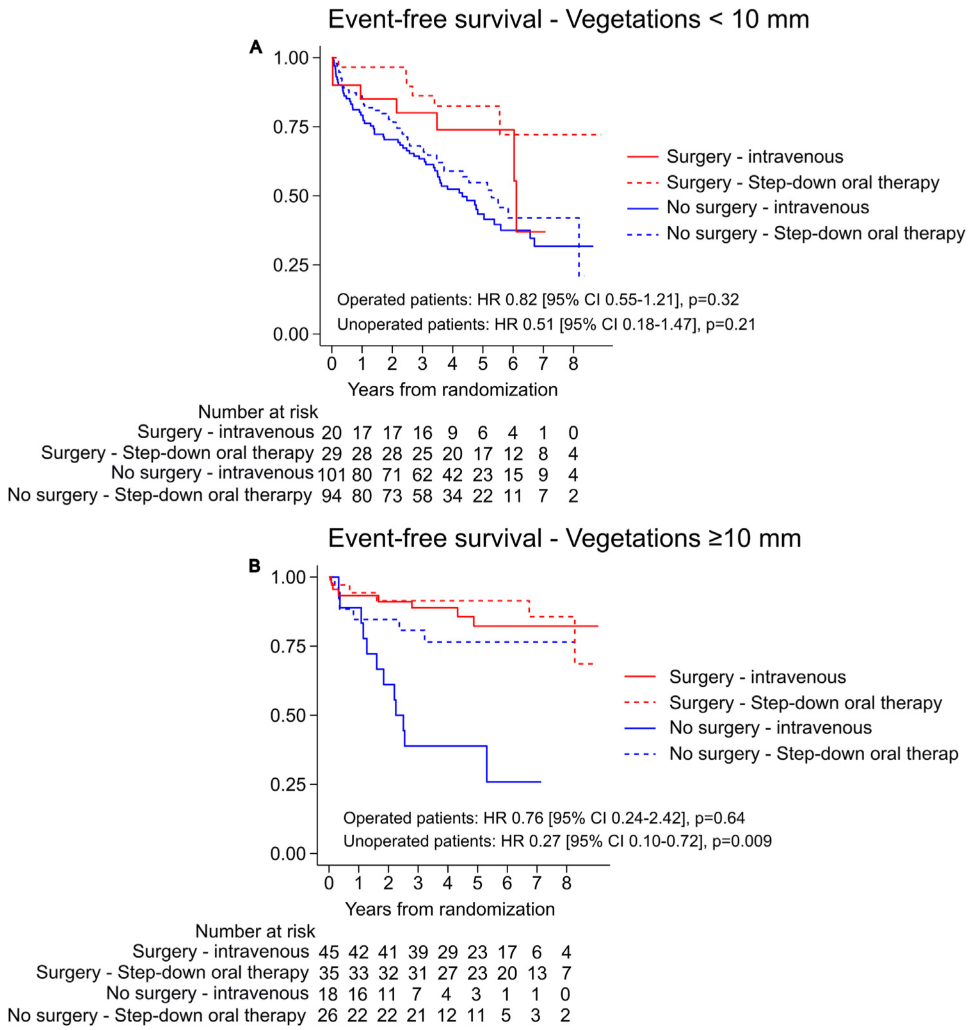

Figure 5. Event-free survival according to vegetation size, IE-related surgery before randomization, and step-down oral therapy Kaplan-Meier curves for freedom from the combined end point according to randomization to intravenous or step-down oral therapy and IE-related surgery before randomization among stable IE patients with a diagnostic TEE finding of (*A*) vegetation size < 10 mm and (*B*) vegetation size ≥ 10 mm. Red bars represent patients with surgery before randomization, and blue bars represent patients without surgery. step-down oral therapy is stand-down oral antibiotic therapy.

contraindications for initiating step-down oral antibiotic therapy.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Rasmus Carter-Storch: Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mia Marie Pries-Heje:** Writing – review & editing, Software, Formal analysis, Conceptualization. **Jonas A. Povlsen:** Writing – review & editing, Project administration. **Ulrik Christensen:** Writing – review & editing, Resources. **Sabine U. Gill:** Writing – review & editing, Investigation. **Julie Glud Hjulmand:** Writing – review & editing, Investigation, Data curation. **Niels E. Bruun:** Writing – review & editing, Investigation. **Hanne Elming:** Writing – review & editing, Investigation. **Trine Madsen:** Writing – review & editing, Investigation. **Kurt Fuursted:** Writing – review & editing, Investigation. **Martin Schultz:** Writing – review & editing, Investigation. **Jens J. Christensen:** Writing – review & editing, Investigation. **Flemming Rosenvinge:** Writing – review & editing, Investigation. **Jannik Helweg-Larsen:** Writing – review & editing, Investigation. **Emil Fosbøl:** Writing – review & editing, Investigation. **Lars Køber:** Writing – review & editing, Investigation. **Christian Torp-Pedersen:** Writing – review & editing, Investigation. **Niels Tønder:** Writing – review & editing, Investigation. **Claus Moser:** Writing – review & editing, Investigation. **Kasper Iversen:** Writing – review & editing, Investigation, Conceptualization. **Henning Bundgaard:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Nikolaj Ihlemann:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.04.058.

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