Challenges in the Diagnostic Process and Management of Infective Endocarditis

Ali Reza Wahadat

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Challenges in the Diagnostic Process and Management of Infective Endocarditis

Uitdagingen in het diagnostisch proces en management van infectieuze endocarditis

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بسمه تعالی

“Everything diminishes when it is used, except knowledge.”
امام علی (ع)

Table of contents

Chapter 1. General introduction 9

Part I – The implementation of the ESC guidelines for Infective Endocarditis

Chapter 2. Implementation of the 2015 European Society of Cardiology Guidelines for the management of infective endocarditis in The Netherlands 23
Netherlands Heart Journal. 2020 Dec;28(12):628-636.

Part II – Multidisciplinary Approach for Infective Endocarditis

Chapter 3. The Impact of the Multidisciplinary Endocarditis Team on the Management of Infective Endocarditis. 39
Neth Heart J. 2022 Jul 4. doi: 10.1007/s12471-022-01707-6.

Chapter 4. Heart team meetings during COVID-19. 55
Eur Heart J. 2020 May 21;41(20):1872-1874. doi: 10.1093/eurheartj/ehaa412.

Chapter 5. Remote multidisciplinary heart team meetings in immersive virtual reality: a first experience during the COVID-19 pandemic. 65
BMJ Innov. 2021 Apr;7(2):311-315. doi: 10.1136/bmjinnov-2021-000662.

Part III – The Value of PET/CT in the Diagnosis of Infective Endocarditis

Chapter 6. Normal Imaging Findings after Aortic Valve Implantation on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography with Computed Tomography. 89
J Nucl Cardiol. 2021 Oct;28(5):2258-2268. doi: 10.1007/s12350-019-02025-y. Epub 2020 Jan 23.

Chapter 7. Normal imaging findings after ascending aorta prosthesis implantation on ^{18} F-Fluorodeoxyglucose Positron Emission Tomography with computed tomography. 105
J Nucl Cardiol. 2021 Oct 27. doi: 10.1007/s12350-021-02826-0.

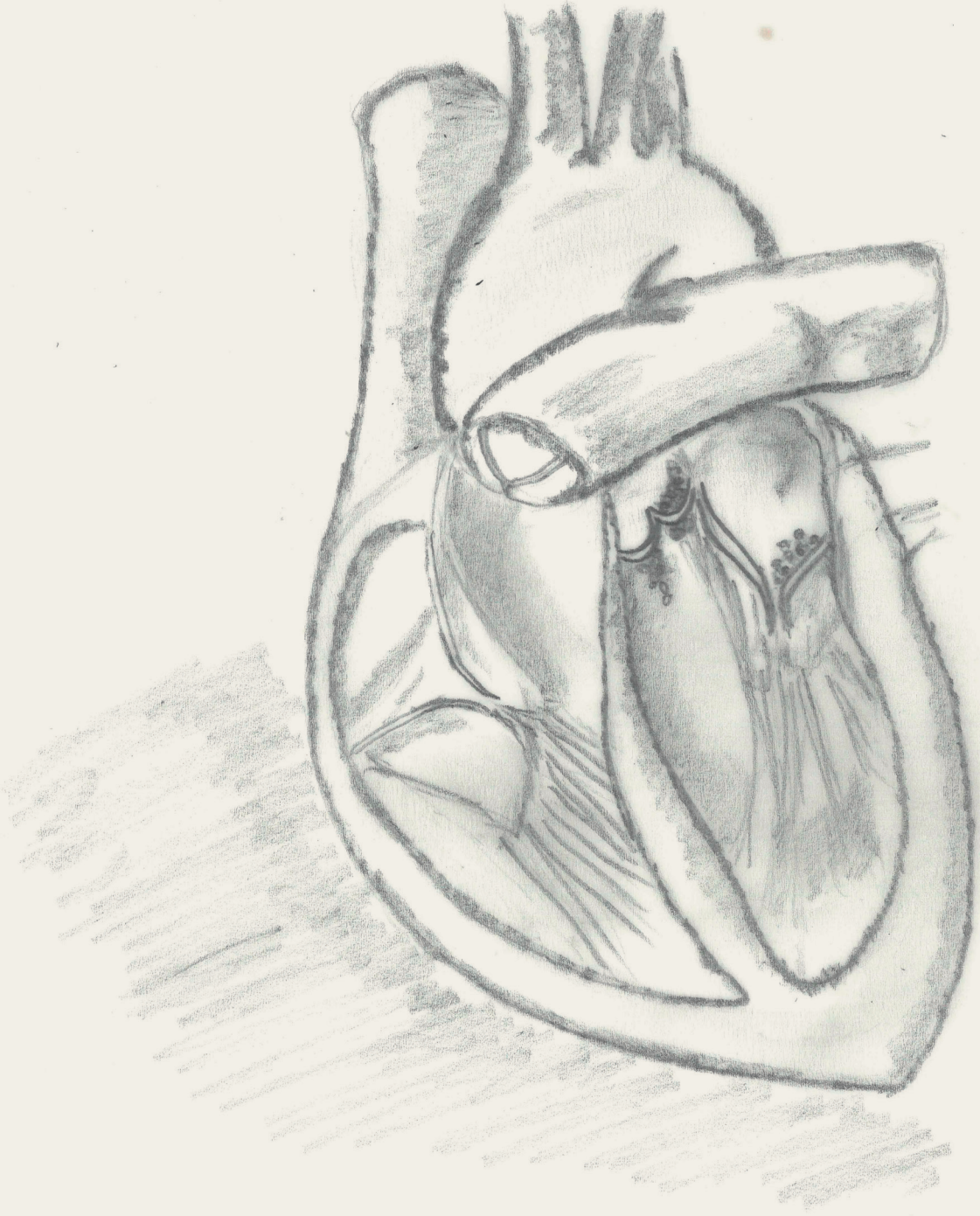
Chapter 8. Added value of ^{18} F-FDG-PET/CT and cardiac CTA in suspected transcatheter aortic valve endocarditis. 121
J Nucl Cardiol. 2021 Oct;28(5):2072-2082. doi: 10.1007/s12350-019-01963-x. Epub 2019 Dec 2.

Part IV – The Value of Cardiac CT in the Diagnosis of Infective Endocarditis

Chapter 9. Screening for coronary artery disease in early surgical treatment of acute aortic valve infective endocarditis. 141
Interact Cardiovasc Thorac Surg. 2021 Apr 19;32(4):522-529. doi: 10.1093/icvts/ivaa313.

Epilogue

Chapter 10. Summary 167
Summary in Dutch | Nederlandse samenvatting 170
General discussion 174
List of publications 183
PhD-portfolio 185
About the author | Curriculum Vitae 187
Acknowledgement | Dankwoord 188



Chapter 1

General introduction

Infective Endocarditis

Infective endocarditis (IE) is one of the oldest and deadliest cardiovascular diseases which involves an infection of the endocardium, usually caused by bacteria (and in some cases by fungi). that These micro-organisms multiply and may subsequently cause local damage to the heart. In most cases the multiplication of the micro-organisms cause attraction of immune system cells which leads to the formation of a lesion known as “vegetation”. This lesion is a mass that consists of micro-organism colonies, fibrin, platelets and inflammatory cells. The heart valves are most commonly involved, however other structures such as the interatrial or interventricular septum (especially in cases of septal defect), the endocardium of the left and the right ventricle or prosthetic material inside the heart can be affected as well. In some cases, the premium part of the infection is outside the heart such as in case of coarctation of the aorta or open ductus arteriosus which can get infected and cause endocarditis-endarteritis. Furthermore, almost all other organs can be affected and damaged by (parts of) the vegetation that can embolize through the bloodstream. The incidence of IE is reported to be 15 per 100.000 patients per year (1) which is relatively low compared to other cardiovascular diseases such as coronary syndromes or heart failure. However, even today endocarditis is still the deadliest cardiovascular disease with a reported high mortality rate of 17% within 2 months and 28% within 6 months of the diagnosis (2, 3). The population at risk for IE has changed in the past years from young patients with rheumatic valve disease to patients with prosthetic heart valves, intra-cardiac devices, intravenous drug abusers and elderly patients (1, 4-6). Nosocomial infections are more frequent and *Staphylococcus aureus* has taken over oral *Streptococci* as the most frequent pathogen causing IE(4, 7). This change in epidemiology makes IE a dynamic disease with new forms of clinical presentation and challenging diagnosis which requires a change in management.

New European Guidelines

In 2015, the European Society of Cardiology (ESC) introduced new guidelines for the management of IE (8). One of the new features in these guidelines was the introduction of a multidisciplinary team for the management of IE. The broad clinical presentation of IE depending on the medical history, involved micro-organism and the potential complication along with needed expertise from practitioners from several specialties were the main reasons to introduce a multidisciplinary Endocarditis Team for a collaborative approach of the management of IE. A few studies demonstrated improvement of survival in patients with IE after introducing the Endocarditis Team in their medical center (9, 10). However, this could partially be explained by the improvement in overall medical care over time, since these studies were not randomized trials but comparisons in historical cohorts. Furthermore,

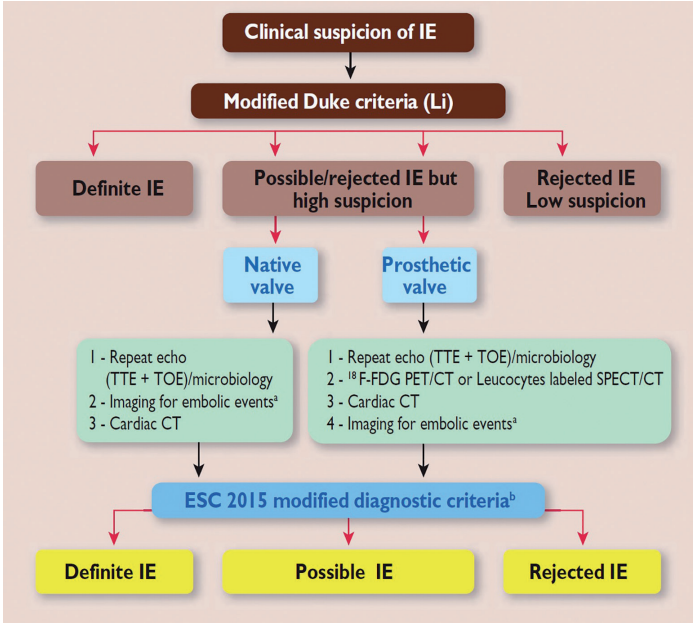
the challenges and pitfalls in setting up an Endocarditis Team along with the impact of this multidisciplinary approach on the policy of IE need further clarification.

Another new feature in the guidelines was the implementation of ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) and cardiac computed tomography angiography (CTA) as new diagnostic imaging tools in patients with suspected IE. IE remains difficult to diagnose due to a broad range of clinical presentation. The Modified Duke Criteria (Table 1) which are commonly used by physicians around the world for the diagnosis of IE, consists of “major" and “minor” criteria (11). The outcome after the use of these criteria is either “definite IE”, “possible IE” or “rejected IE”. The diagnosis of definite IE is made when there are 2 major criteria, 1 major and 3 minor criteria or 5 minor criteria. In case that there are 1 major and 1-2 minor criteria or 0 major and 3-4 minor criteria the diagnosis is possible IE. The diagnosis of IE is rejected when there are only 2 or fewer minor criteria. Positive blood cultures are the cornerstone of the diagnosis and a major criterion in the Modified Duke Criteria. Patients are usually suspected for IE after an

Table 1: Modified Duke criteria according to

Major Criteria
Blood culture positive for IE • Typical microorganisms consistent with IE from 2 separate blood cultures: - Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or - Community-acquired enterococci, in the absence of a primary focus; or • Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: - At least 2 positive cultures of blood samples drawn 112 h apart; or - All of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart) • Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer 11 : 800 Evidence of endocardial involvement Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least “possible IE” by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows : Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or Abscess; or New partial dehiscence of prosthetic valve New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor Criteria
• Predisposition such as predisposing heart condition, or injection drug use. • Fever defined as temperature >38°C. • Vascular phenomena, major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway’s lesions. • Immunological phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor. • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

unexplained bacteremia. However, blood cultures could be negative for multiple reasons such as antibiotic use prior to culture or the type of micro-organism involved with the infection (12, 13). Therefore, the timely diagnosis of IE depends also on the correct interpretation of the echocardiogram (the second major criterion). However, the interpretation of lesions on transthoracic as well as transesophageal echocardiography appear to be limited in case of prosthetic valve endocarditis (PVE) and cardiac device related infective endocarditis (CDRIE) compared to native valve endocarditis (NVE) (14, 15). That is why the 2015 ESC guidelines introduced the use of 18F-FDG PET/CT and CTA as additional diagnostic imaging tools for the diagnosis of IE especially of PVE (Figure 1) (8). The use of PET/CT is recommended in the guidelines in patients with suspected PVE, who had their prosthetic valve implantation >3 months earlier, and of whom the diagnosis could not be confirmed with the use of the Modified Duke Criteria. A positive PET/CT should then be interpreted as a major criterion for the diagnosis of IE. However, the guidelines do not mention the criteria for a positive PET/CT due to lack of data in the literature. Furthermore, the guidelines advise to adhere a 3 months safety period after surgery before performing a PET/CT to detect PVE. This is



CT = computed tomography; FDG = fluorodeoxyglucose; IE = infective endocarditis; PET = positron emission tomography; SPECT = single photon emission computerized tomography; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.
[a]May include cerebral MRI, whole body CT, and/or PET/CT.
[b]See Table 14.

Figure 1: European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis.
Image courtesy of Habib G et al. Eur Heart J. 2015;36(44):3075-128. (8)

in order to prevent false interpretation of possible physiological FDG uptake after surgery due to a normal healing response. However, this is based on expert opinion and not substantiated by scientific research since there was no good data. Since the introduction of the ESC guidelines in 2015, multiple new studies provided additional information to the value of PET/CT for the diagnosis of IE (16-18). In 2018 Swart et al provided a cut-off value for semi-quantitative measurements of pathologic FDG uptake around the prosthetic valve which helps to improve the sensitivity and specificity of PET/CT for the diagnosis of PVE (18). In this same work, Swart et al also provided PET/CT results of patients with prosthetic heart valves who had underwent the scan for other reasons than infection/endocarditis, such as diagnostic work up of oncological diseases. However, prospective data about the normal FDG uptake pattern and intensity around the prosthetic valve or around the intra cardiac devices remained absent. Furthermore, the guidelines did not mention the use of PET/CT in patients with additional prosthesis of the aortic root and ascending aorta. These prostheses can be infected solely or additionally in cases of PVE and have devastating consequences. For these prostheses as well, the normal FDG uptake after implantation is not reported in the literature. These normal FDG uptakes for prosthetic valves and ascending aorta prosthesis would help clinicians interpret the PET/CT images in patients with suspected IE.

CTA is also a promising imaging tool for the diagnosis of IE, especially in cases with a prosthetic valve and suspicion of aortic root abscess (19-21). Due to the acoustic shadowing originated by metallic structures used in prosthetic heart valves some parts of the heart cannot be visualized during echocardiography, which can cause missing important information, such as anatomical complications of IE. CTA is not limited by acoustic shadowing and provides outstanding anatomical information from multiple views which can be presented dynamically. Key anatomical information such as the size, location and contact with other structures for aortic root abscesses or mycotic aneurysms can so be provided to cardiologists and cardiac surgeons which can help them in correct diagnosis and preparation for surgery. Along with the detection of vegetations and other complications of IE, CTA is a useful tool to detect coronary artery disease (CAD), especially in patients with a vegetation on the aortic valve in whom coronary angiography may be risky since there is chance of embolization. However, the added value of CTA in detection CAD in patients with IE of the aortic valve needs to be clarified.

Complex patients

Transcatheter aortic valve implantation (TAVI) is nowadays increasingly applied for the treatment of aortic valve stenosis in selected patients (22). PVE can occur after a TAVI (TAV-IE) and cause devastating complications which can lead to patients' death. Timely diagnosis of TAV-IE is important; however, the diagnosis is difficult when relying on the modified Duke

criteria. A multimodality imaging approach for the diagnosis of TAV-IE with the use of PET/CT and CTA could be helpful. However, data about the diagnostic value of these two imaging techniques in addition to the modified Duke criteria is still very scarce.

Left ventricular assist device (LVAD) can improve quality of life and long-term survival in patients with end-stage heart failure and is increasingly used in the treatment of such patients. These patients have a complex medical history with often multiple prosthetic materials/devices implanted in their thorax. Infection of these devices can cause severe problems which can become life-threatening and so early and precise detection of the infected parts are of the essence. However, in case of suspicion of infection distinguishing the infected devices from the non-infected devices is difficult as conventional imaging modalities such as echocardiography and CT are hampered by device-related artefacts. FDG-PET/CT can be used for establishing the diagnosis of LVAD infection (23, 24). However, it may be possible to increase its diagnostic accuracy in LVAD specific infections by clarifying confounding factors and the use of semi-quantitative analysis. IE cases can be complex and difficult to diagnose. Especially with the presence of multiple imaging modalities such as transthoracic and transesophageal echocardiography (TTE/TEE), CTA and PET/CT, the demand for current knowledge in different aspects of these techniques is increasing. Therefore, more studies are required to provide an overview of the strength, weaknesses and pitfalls of these imaging techniques.

COVID-19 and new forms of communication

Due to the coronavirus disease 2019 (COVID-19), governments all over the world installed gathering restrictions in order to prevent further spread of the disease. Because of this the working condition and the way of communication changed throughout the whole world (25-27). Multidisciplinary meetings, such as the Endocarditis Team, could not be adhered safely and according to the gathering restriction rules. New ways of safe and useful communication had to be implemented. Virtual reality (VR) has shown promising and interesting results as an emerging new way of communication between physicians (28, 29). VR might be a useful way of communication by clinicians attending a multidisciplinary meeting.

Outline of the thesis

This thesis puts further emphasis on the value of the multidisciplinary approach for the management of IE, especially during the COVID-19 pandemic. It provides normal PET/CT images after prosthetic valve implantation and explores the additional diagnostic value of PET/CT and cardiac CTA in the diagnosis of infective endocarditis. In addition, it analyses the role of CTA in the detection of coronary disease in patients with IE.

Part I addresses the implementation of the most recent European guidelines for infective endocarditis in the Netherlands (Chapter 2).

In part II, data of 4 years of experience with the Endocarditis Team is provided from a prospective registry (Chapter 3) followed by the adaptation of the multidisciplinary approach in times of the COVID-19 pandemic (Chapter 4) and a new way of communication for physicians in multidisciplinary setting through virtual reality (Chapter 5).

In part III, results of our study regarding post-operative findings on PET/CT following an uncomplicated aortic valve replacement (Chapter 6) and the results of post-operative findings on PET/CT after an aortic valve including an ascending aorta (i.e., Bentall procedure) are presented (Chapter 7). In these studies, we aimed to both acquire an idea of normal post-operative PET/CT findings as well as to provide the right time-limit after surgery in what PET/CT can be used correctly. In addition, we provided the additional diagnostic value of PET/CT in specific groups of patients with two multicenter retrospective studies: this was the case for patients with left ventricular assist device (LVAD) related infection (Chapter 8) and for patients with suspected endocarditis of transcatheter implanted aortic valve (TAVI) (Chapter 9).

Finally, in part IV, we aim to provide the value of cardiac CTA in detection of coronary artery disease in patients with endocarditis of the aortic valve (Chapter 10).

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PART I

The implementation of the ESC guidelines for Infective Endocarditis


ESC

Chapter 2

Implementation of the 2015 European Society of Cardiology Guidelines for the management of infective endocarditis in The Netherlands

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Abstract

Because the occurrence of infective endocarditis (IE) continues to be associated with high mortality, a working group was created by the Dutch Society of Cardiology to examine how the most recent European Society of Cardiology (ESC) guidelines for IE management could be implemented most effectively in the Netherlands. In order to investigate current Dutch IE practices, the working group conducted a country-wide survey. Based on the results obtained, it was concluded that most ESC recommendations could be endorsed, albeit with some adjustments. For instance, the suggested pre-operative screening and treatment of nasal carriers of *Staphylococcus aureus* as formulated in the ESC guideline was found to be dissimilar to current Dutch practice, and was therefore made less restrictive. The recently adapted ESC diagnostic criteria for IE were endorsed, while the practical employment of the relevant diagnostic techniques was simplified in an adapted flowchart. In addition, the presence of a multidisciplinary, so-called 'endocarditis team' in tertiary centers was proposed as a quality indicator. An adapted flowchart specifically tailored to Dutch practice for microbiological diagnostic purposes was constructed. Lastly, the working group recommended the *Stichting Werkgroep Antibioticabeleid* (SWAB; Dutch Working Party on Antibiotic Policy) guidelines for IE treatment instead of the antibiotic regimens proposed by the ESC.

Background and introduction

One of the oldest cardiac diseases, infective endocarditis (IE), remains one of the most fatal manifestations of heart disease (1). Despite considerable progress in diagnosis and treatment, the in-hospital mortality of IE continues to be about 20%, essentially unchanged during the past decades (2).

The importance of IE is reflected in the frequent publication of new guidelines, for instance by the European Society of Cardiology (ESC) (1). In 2017, the Dutch Society of Cardiology created a working group – funded by the Quality Foundation of the Dutch Medical Specialists (SKMS) - to investigate whether and how the recommendations summarized in the most recent ESC guidelines on IE could be implemented most effectively in the Netherlands. To investigate current Dutch IE practices, the working group conducted a short country-wide survey. The medical topics raised in the survey are presented in Table 1. This report summarizes the findings and recommendations of the working group.

Prevention and prophylaxis

Although widespread antibiotic prophylaxis for IE has long been considered effective, the policy for liberal use of antibiotic prophylaxis has gradually changed to more restricted indications. Of note, the 2008 guidelines of the National Institute of Health and Clinical Excellence (NICE) from the UK recommended that antibiotic prophylaxis should be abandoned completely (3). However, this recommendation was revised after a patient with aortic valve prosthesis died from IE after undergoing a dental procedure without - in line with the NICE guidelines - the use of prophylaxis. The NICE guidelines from 2016 recommend the dentists to inform the patient about the level of risk and let him or her decide whether or not to receive antibiotic prophylaxis (4). The strategy currently endorsed by the American College of Cardiology (ACC), American Heart Association (AHA) and ESC reserves antibiotic prophylaxis for individuals with cardiac disease at high risk of IE, e.g., for patients with a prosthetic valve, a history of IE, or with cyanotic congenital heart disease undergoing a dental procedure with a high risk of bacteremia (usually involving perforation of the gingiva) (1, 5). Of course, proper oral hygiene is strongly promoted universally. The working group decided to endorse the recommendations of the ESC guidelines on prophylaxis in high-risk subjects without changes or comments (1).

Nasal carriers of *Staphylococcus aureus* have more infections after cardiac surgery (6), and the pre-operative eradication of this micro-organism is thus important. To this end, two options are available. In the first, all subjects – without additional testing – are treated locally with an antibiotic ointment, usually mupirocin. Another option is to screen every patient,

Table 1 Selection of recommendations by the working group with regard to the European Society of Cardiology (ESC) guidelines.

Topic	Recommendations in ESC guidelines	Recommendation by the working group
Antibiotic prophylaxis	Reserve antibiotic prophylaxis for high-risk individuals undergoing dental procedures	No change or comment by the working group
Prevention of infection before cardiac or vascular interventions	Screen every patient and treat *Staphylococcus aureus* carriers only pre-operatively	Pre-operative screening and/ or treatment of nasal carriage of *Staphylococcus aureus* is recommended before elective surgery in order to treat carriers[a]
Microbiological diagnosis	Use the recommendation as presented in the ESC guidelines	Use flowchart as presented in Fig. 1[a]
Diagnostic imaging and criteria	Use diagnostic ESC criteria and the recommendation presented in the guidelines	Use diagnostic ESC criteria and the flowchart as presented in Fig. 2[a]
Endocarditis team	Centres without cardio-thoracic facilities must consult the regional endocarditis team in cases of (suspected) IE.	No change or comment by the working group
Antimicrobial therapy	Antimicrobial therapy according to the ESC guidelines	Antimicrobial therapy according to SWAB guidelines[a]
Surgery	Indication and timing of surgery as presented in the guidelines	No change or comment for the indication of surgery Timing of surgery determined by the specialists involved[a]
Discharge	Transthoracic echo after completion of therapy Regular follow-up including blood samples Good oral health maintenance	No change or comment by the working group

SWAB Stichting Werkgroep Antibioticabeleid (Dutch Working Party on Antibiotic Policy)
[a] Different recommendation made by the working group compared with the ESC guidelines

and to treat *S. aureus* carriers only. The ESC guidelines recommend only the latter procedure. But the merits of the two methods are of course comparable, and this is - according to the survey - reflected by the concomitant use of both approaches for decolonization of *S. aureus* in Dutch hospitals. Therefore, the text of the recommendation in Table 7 of the guidelines was (slightly) adapted as follows: 'Preoperative screening and/or treatment of nasal carriage of *Staphylococcus aureus* is recommended before elective cardiac surgery in order to treat carriers', while the last recommendation of the same table ('Systemic local treatment without screening of *Staphylococcus aureus*' is not recommended) was deleted.

Microbiological diagnosis

Positive blood cultures remain the cornerstone of IE diagnosis. At least three sets with sufficient volume should be taken at 30-min intervals, and sampling preferably be obtained from a peripheral vein. When a micro-organism has been identified and appropriate antimicrobial treatment is commenced based on susceptibility results, blood cultures should be repeated every 48-72 h until blood cultures remain sterile to verify the effectiveness of the therapeutic regimen. Blood-culture-negative IE refers to IE in which no causative micro-organism can be identified using standard culture methods. In such instances, bacteria such as *Bartonella* spp. or *Coxiella burnetii*, fungi or fastidious bacteria may be in play and additional diagnostic testing may be required. Table 12 and Fig. 2 in the ESC guidelines refer to these circumstances. However, some microbiological tests included therein are not available in the Netherlands. The working group has therefore developed a flowchart adapted to Dutch practice (Fig. 1).

Diagnostic imaging and criteria

While the modified Duke criteria, which rely heavily on positive blood cultures and findings compatible with IE at echocardiography (7), remain the mainstay for diagnosing IE, current guidelines reflect the increasing importance of more advanced imaging techniques (1). In particular, computed tomography (CT), positron emission tomography with CT (PET-CT) and magnetic resonance imaging have emerged as valuable additional imaging techniques that provide complementary diagnostic information to echocardiography (1). Available data – also from the Netherlands - indicate increased diagnostic accuracy when these techniques are added to the modified Duke criteria, especially in prosthetic valve endocarditis (PVE) (8-10). The guidelines provide detailed recommendations on the use of various imaging techniques in both native valve IE and PVE, as well in the diagnosis of cardiac-device-related endocarditis [7, 8]. The working group has combined the text and figures that describe these recommendations in the ESC guidelines into a single scheme (Fig. 2).

The diagnostic accuracy of the modified Duke criteria – which merge the presence of an infective syndrome and endocardial involvement, classically employing echocardiography – is only moderate, in particular in IE of a prosthetic valve (1, 11, 12). Advanced imaging techniques – as described above – may not only be helpful in the detection of endocardial lesions when added to echocardiography, but also in establishing the presence of (clinically silent) vascular phenomena such as embolic events and infectious aneurysm (13). Acknowledging this, the most recent ESC guidelines have added the identification of paravalvular lesions by CT and, in the setting of PVE, abnormal activity near the site of the prosthesis on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT or radiolabeled leucocyte

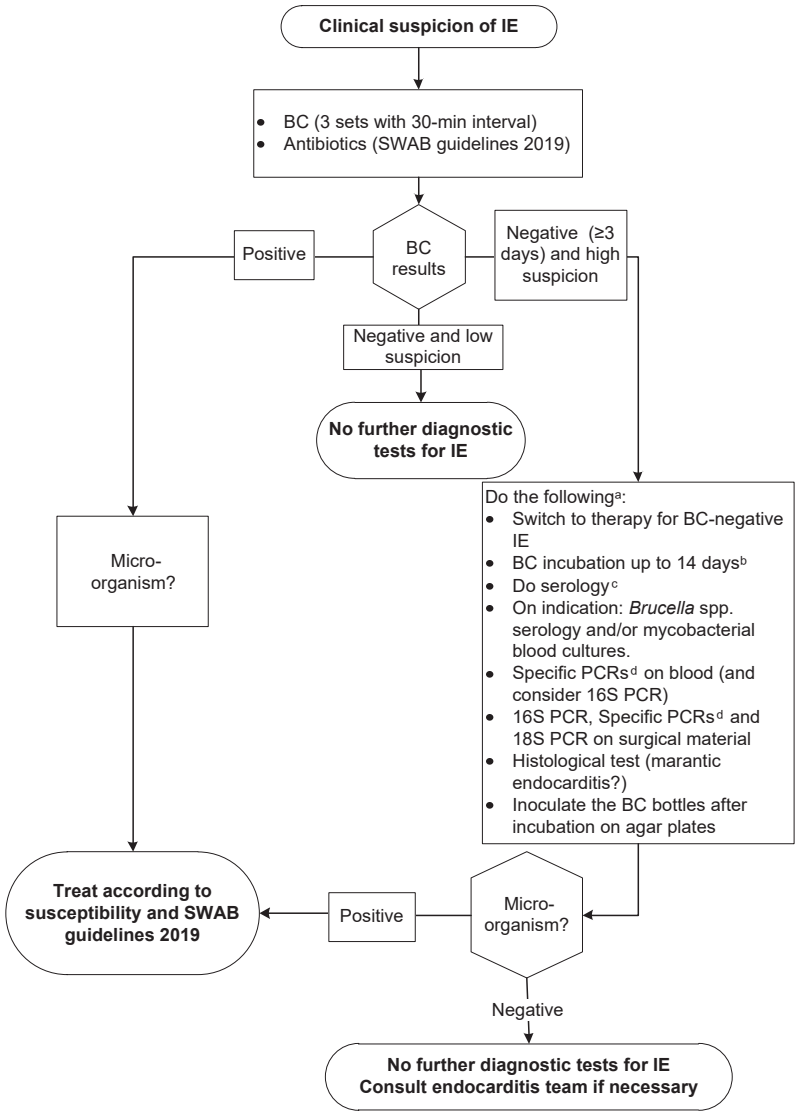

Fig. 1 Flowchart of microbiological tests for infective endocarditis in The Netherlands.

IE Infective endocarditis, *BC* blood cultures, *SWAB Stichting Werkgroep Antibiotica Beleid* (Dutch Working Party on Antibiotic Policy), *PCR* polymerase chain reaction

[a] If the diagnostic test is not available, send the blood samples and/or blood cultures to a reference laboratory

[b] So as not to miss *Cutibacterium acnes* and/or if blood cultures were drawn while receiving antimicrobial therapy

[c] *Bartonella* spp. (IgM, IgG), *Coxiella burnetii* (including indirect immunofluorescent assay phase I IgG), *Legionella* spp. (IgM, IgG), *Mycoplasma* spp. (IgM, IgG)

[d] Specific PCRs: *Bartonella* spp., *Coxiella burnetii*, *Legionella* spp., *Mycoplasma* spp., *Tropheryma whipplei*

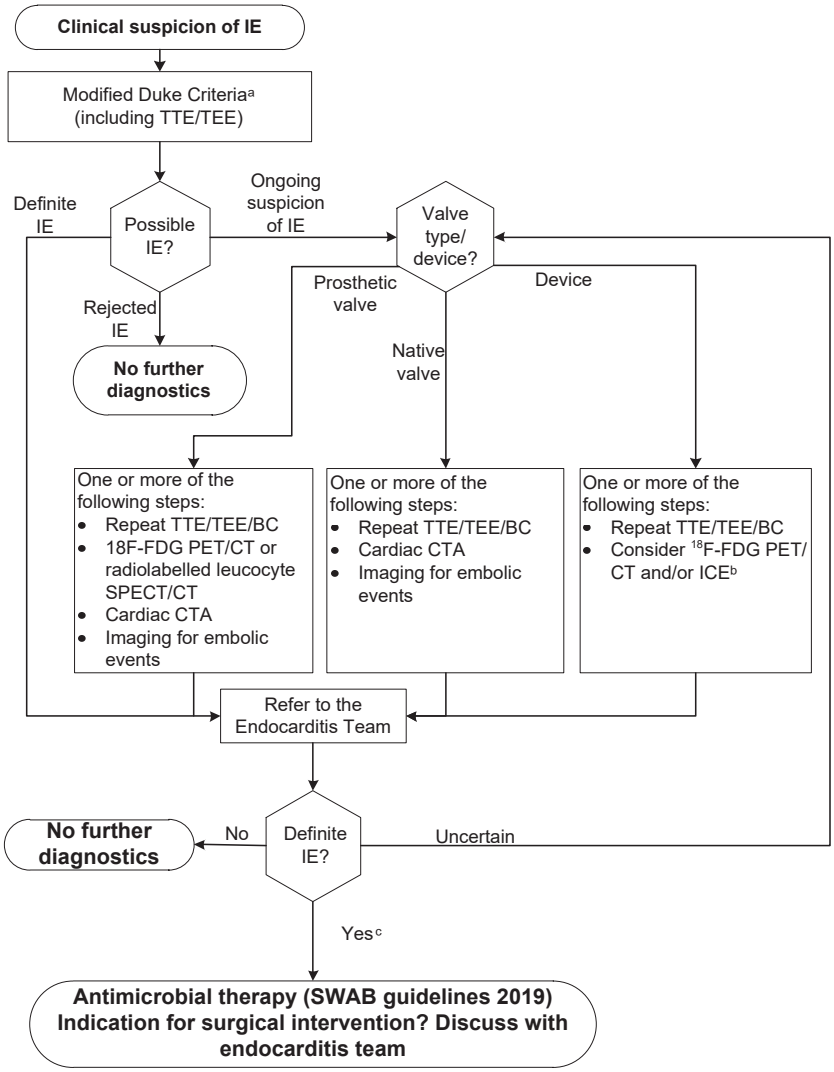

Fig. 2 Flowchart of diagnostic imaging for infective endocarditis in the Netherlands.

IE infective endocarditis, *TTE* transthoracic echocardiogram, *TEE* transoesophageal echocardiogram, BC blood cultures, *^{18}F-FDG PET/CT* ^{18}F-fluorodeoxyglucose positron emission tomography computed tomography, *SPECT* single photon emission computed tomography, ICE intracardiac echocardiogram, *SWAB Stichting Werkgroep Antibiotica Beleid* (Dutch Working Party on Antibiotic Policy)

[a] [(1, 25)

[b] (26)

[c] Consider referring to a tertiary referral center when there is definite IE and one or more of the following: congenital heart disease in pregnancy, prosthetic valve endocarditis, heart failure, perivalvular extension or uncontrolled infection, embolic events or cerebrovascular accident, arrhythmia or conduction disturbances

CTA: Computed tomography angiography

single photon emission computerized tomography (SPECT)/CT, as a 'major' criterion for IE. The currently applicable two major and five minor criteria for IE are described in Table 2. Examples of positive echocardiogram, ^{18}F-FDG PET/CT and cardiac CT are demonstrated in Fig. 3.

Table 2 Diagnostic criteria for infective endocarditis (IE) according to the 2015 European Society of Cardiology (ESC) guidelines for IE

Major criteria
1. Blood cultures positive for IE a. Typical micro-organisms consistent with IE from 2 separate blood cultures: • Viridans streptococci, *Streptococcus gallolyticus (Streptococcus bovis)*, HACEK group[a], *Staphylococcus aureus*; or • Community-acquired enterococci, in the absence of a primary focus; or b. Micro-organisms consistent with IE from persistently positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart; or • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or c. *Coxiella burnetii* phase I IgG antibody titre >1:1024
2. Imaging positive for IE a. Echocardiogram positive for IE: • Vegetation • Abscess, pseudoaneurysm, intracardiac fistula • Valvular perforation or aneurysm • New partial dehiscence of prosthetic valve b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for > 3 months) c. Paravalvular lesions and/or vegetation detected by cardiac CTA
Minor criteria
1. Predisposing heart condition or injection drug use 2. Fever defined as temperature >38°C 3. Vascular phenomena (including those detected by imaging only) 4. Immunological phenomena (e.g. Janeway lesions, Osler's nodes) 5. Positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
Definite IE • Clinical criteria: 2 major or 1 major + 3 minor or 5 minor criteria • Pathological criteria: microorganism cultures from the vegetation or confirmed by histological examination of vegetation/intra-cardiac abscess showing active endocarditis Possible IE • Clinical criteria: 1 major + 1 minor or 3 minor criteria

Data partially derived from the 2015 ESC guidelines for IE [1]
IE infective endocarditis, *^{18}F-FDG* ^{18}F-fluorodeoxyglucose, *PET/CT* positron emission tomography/computed tomography, *CTA* computed tomography angiography
[a] *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*

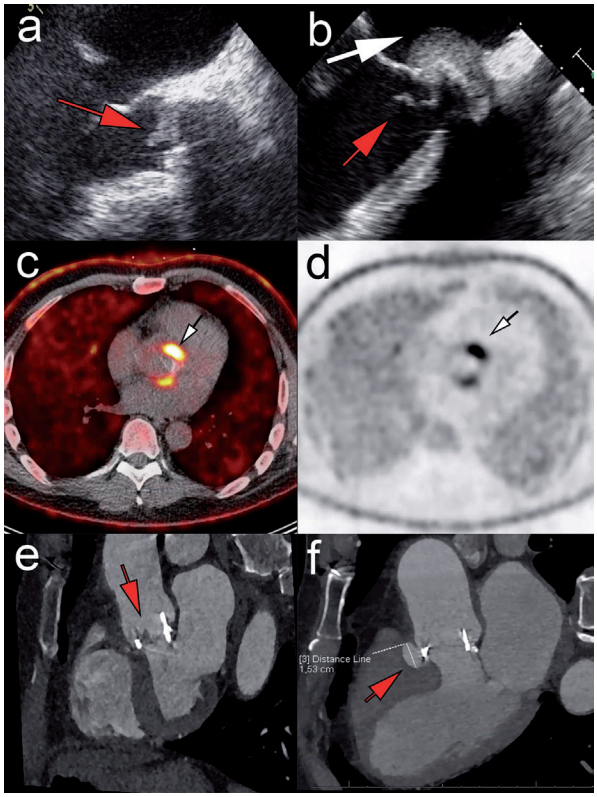

Fig. 3 Different examples of major imaging diagnostic criteria: two cases of positive transesophageal echocardiogram (**a, b**), one case of positive ^{18}F-FDG PET/CT (**c, d**) and one case of positive cardiac CT (**e-f**).

a A case of a mechanical aortic valve with signs of vegetation (*red arrow*). The *red arrow* in **b** also indicates a vegetation on the aortic valve bioprosthesis, whereas the *white arrow* indicates a possible abscess of the aortic root. In **c** (fused PET/CT images) and in **d** (non-attenuated PET images) the *white* arrows indicate ^{18}F-FDG uptake around the aortic valve bioprosthesis as a sign of possible infection. The *red arrow* in **e** indicates a vegetation on one of the leaflets of an aortic valve bioprosthesis. Finally, the *red arrow* in **f** indicates a mycotic aneurysm alongside the aortic valve bioprosthesis

The 'endocarditis team'

An important addition in the latest ESC guidelines is the recommendation to establish a multidisciplinary 'endocarditis team'. Such a team, comprising – at least – a cardiologist, cardio-thoracic surgeon, infectious diseases specialist, microbiologist and radiologist/nuclear medicine physician should provide the expertise needed to treat complex IE patients. The guidelines refer – amongst other things – to the team approach adopted in France, with standardized medical therapy and uniform recommendations for surgical interventions that were found to improve outcome relative to earlier experience (14-18). A comparable recommendation has been made in the AHA/ACC guidelines for the management of patients

with valvular disease (19). In line with the ESC guidelines, the working group recommended that each of the current 16 Dutch tertiary referral centers with cardio-thoracic facilities create a specific regional endocarditis team. Moreover, the working group proposed to qualify the presence and composition of such a team as a quality indicator. The working group endorsed the ESC guidelines recommendation that centers without cardio-thoracic facilities must consult the regional endocarditis team in cases of (suspected) IE.

Antimicrobial therapy

There are major differences between European countries in the use of antimicrobial therapy and consequently in the antibiotic resistance patterns of pathogens. The Netherlands has the lowest rate of antibiotic use in Europe. The result is a stable level of antimicrobial resistance, whereas most countries experience increasing levels each year. European guidelines for antimicrobial therapy therefore cannot be simply adhered to but have to be tailored to individual countries. Recommendations for antibiotic therapy in the Netherlands are provided by the *Stichting Werkgroep Antibiotica Beleid* (SWAB; Dutch Working Party on Antibiotic Policy). Importantly, SWAB recently updated their guidelines for antibiotic treatment for IE, on the basis of an in-depth comparison of the most recent ESC and the AHA IE guidelines. In cases of discordance between the recommendations in these documents, SWAB guidance is based on a formal literature review on best current Dutch practice, taking into consideration national resistance patterns and dosing habits. For all these reasons, the working group recommended the employment of the SWAB guidelines for subsequent use in the Netherlands (20).

Main complications and their management

Heart failure resulting from valvular regurgitation or obstruction, uncontrolled infection and embolic events occurring under adequate antibiotic treatment constitute major complications of IE and may require surgical treatment (1, 21-24). The working group endorsed the ESC indications for cardiac surgery without modifications. However, the timing of the surgical procedure was left to the discretion of the specialists involved. In accordance with the recommendations of the ESC guidelines, complex IE patients should be referred early to a regional center with cardio-thoracic facilities. Such cases include, but are not limited to, IE patients with congenital heart disease, PVE, pregnant women, patients with heart failure, uncontrolled infection, rhythm abnormalities or stroke.

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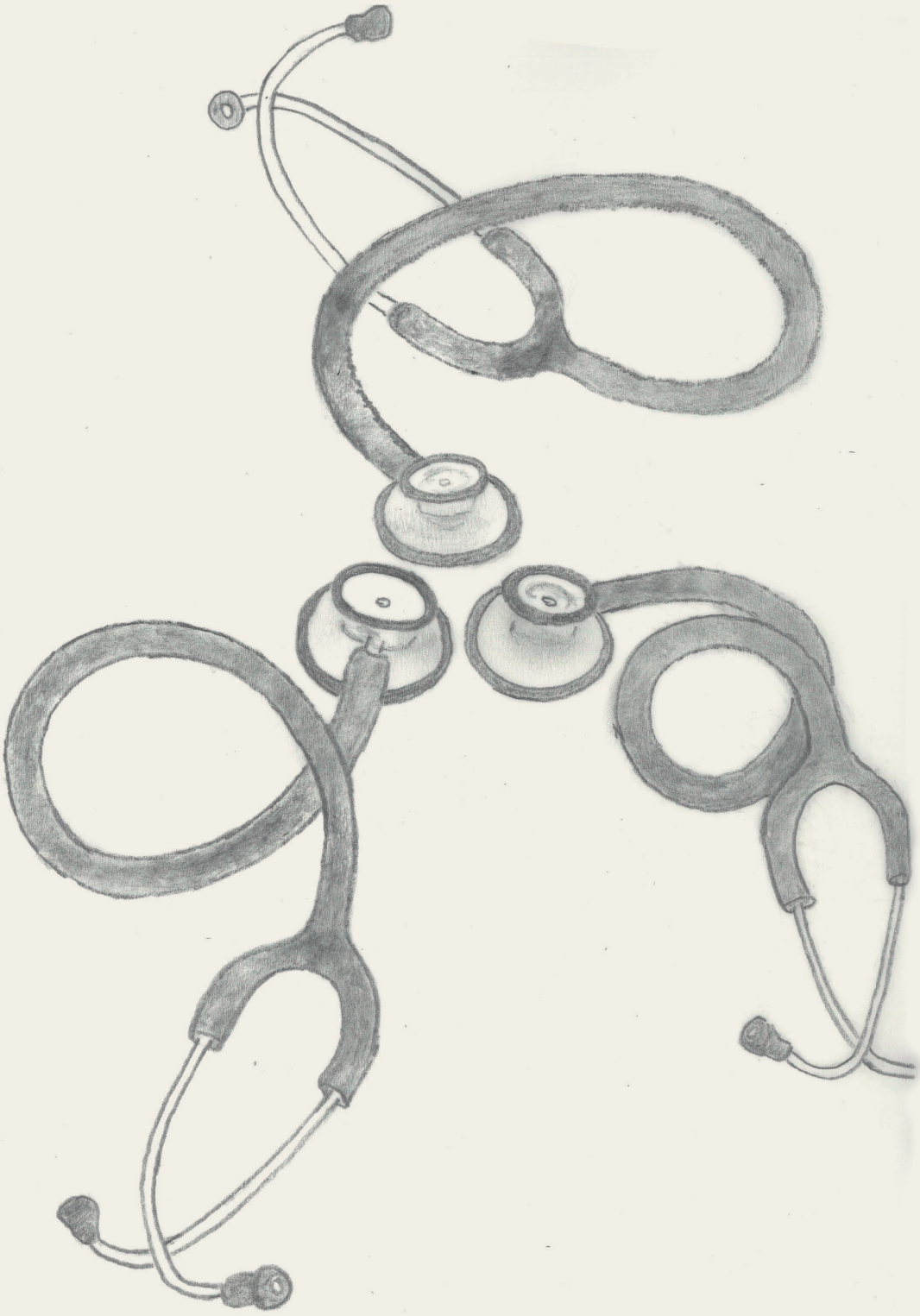
PART II

Multidisciplinary Approach for Infective Endocarditis



Chapter 3

The Impact of the Multidisciplinary Endocarditis Team on the Management of Infective Endocarditis

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The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Abstract

Background: The European Society of Cardiology (ESC) introduced in their latest guidelines for infective endocarditis (IE)(2015) the implementation of the Endocarditis Team (ET) to facilitate the management of IE. This study presents our experiences and the diagnostic and therapeutic impact of the ET on the management of IE.

Methods: From 2016-2020, data of all patients with suspected IE referred to the ET were prospectively collected. The final diagnosis was defined by the ET as either rejected, possible or definite IE. Diagnostic impact was scored as any change in initial diagnosis, the frequency of additional diagnostic tests advised by the ET and any change in diagnosis after these tests. Therapeutic impact was scored as any change in antibiotic therapy or change from conservative to invasive therapy or vice versa.

Results: A total of 321 patients (median age 67[55-77] years, 71% male) were enrolled. The final diagnosis was rejected IE in 47(15%), possible IE in 34(11%) and definite IE in 240(75%) patients. A change of initial diagnosis was seen in 53/321(17%) patients. Additional microbiological tests were advised in 69/321(21%) patients, and additional imaging tests in 136/321(42%) patients, which resulted in sub sequential change in diagnosis in 23/321(7%) patients. Any change in antibiotic treatment was advised in 135/321(42%) patients, and change from initial conservative to additional surgical treatment in 15/321(5%) patients.

Conclusion: The ET had a clear impact on the policy of patients with suspected IE and is of help in the management of this life-threatening disease. Broad implementation is warranted.

Introduction

Despite ongoing improvements in diagnosis and treatment, infective endocarditis(IE) remains associated with high morbidity and mortality (1-5). Due to the intricacy of the disease and its treatment, management by a single practitioner will be suboptimal (6).

A multidisciplinary approach of IE can help decrease its mortality(7, 8)and therefore, the European Society of Cardiology (ESC) advocates the installment of a "Endocarditis Team" (ET) in every reference center (1). After this recommendation by the ESC, other studies have shown the importance of the ET by reporting mortality reduction after its implementation (9, 10). However, data about how the ET exactly influences the management of IE and if so, to what extend it changes the initial diagnostic and therapeutic policy has not been reported.

This paper presents our experiences of our ET in the first 4 years after initiation in order to provide detailed information about its impact on the management of IE.

Methods

Setting up the Endocarditis Team

In 2016, the ET was instated at our institution, comprising of at least a cardiologist with particular expertise in echocardiography, a cardiothoracic surgeon, a medical microbiologist or infectious disease specialist, a cardiovascular radiologist, a nuclear medicine physician and a coordinator. All regional cardiologists were informed about the ET by a letter and by an e-mail newsletter to the regional society of cardiologists, both containing information on how to refer patients to our team. Initially, the referring cardiologist sought contact by phone or email, followed by written information about the case in the form of a letter. In addition, all available images of the diagnostic tests such as transthoracic- and transoesophageal echocardiography (TTE/TOE), cardiac computed tomography angiography (CTA) and positron emission tomography with computed tomography (PET/CT) were sent to the ET.

Regular sessions were planned biweekly and additional ad-hoc sessions were planned in urgent cases.

Data registration

All patients discussed in the ET were prospectively anonymously entered into a database. The final diagnosis was decided by the ET to either be rejected, possible or definite IE at the end of all ET meetings. Patients with a final diagnosis of definite IE were divided into three groups (group 1: native; group 2: prosthetic valves/prostheses; group 3: cardiac

devices). Patients with both native and prosthetic valve infection or both cardiac device and prosthetic valve infection, were included in group 2. Patients with both native valve and cardiac device infection were included in group 3. Information on patient follow up was derived from the electronic patient records. Follow up time was defined as the period between the discussion date until the date of the last notation in the clinical records. Relapse was defined as recurrence of IE by the same microorganism and within 6 months after the first episode. Re-infection was defined as recurrence after 6 months. Data about mortality was derived from the Central Bureau for Statistics (CBS) database. The need for informed consent was waived by the local medical ethics committee.

Diagnostic and therapeutic impact

Diagnostic impact was scored as the number of reclassified patients (rejected, possible and definite IE). If a diagnosis was not provided beforehand by the referring physician, the final diagnosis by the ET was not scored as a reclassification. However, if the additional diagnostic tests advised by the ET did change the initial diagnosis by the ET in the first meeting, this was scored as reclassification.

Therapeutic impact was scored as the combination of any change in antibiotic therapy and/or change to either conservative or invasive treatment due to (additional diagnostic tests advised by) the ET.

Statistics

Descriptive statistics were used for the analyses of the main outcomes. Categorical variables were reported as numbers and percentages whereas continuous variables were reported as mean±SD or medians and interquartile ranges (IQR). Non-parametric statistical analyses (Mann Whitney-U test) were performed for the comparison of two continuous variables. The Kruskall Wallis test was used for comparison of >2 continuous variables, and for categorical variables the Chi-square (X^2) test was performed to determine differences between groups. Kaplan-Meier curve plots for time to all-cause mortality and time to rate of relapse/re-infection were made, and a Log-Rank test was performed to demonstrate the difference between groups for either survival or relapse/re-infection. A significance level of p=0.05 were used.

Results

Between January 2016 and January 2020, 321 unique patients (median [IQR] age 67 years [55-77], male: n=228, 71%) with suspected IE from 10 different medical centres (95/321, 29.5% from our own centre) were referred to our ET. None of the other participating hospitals had implemented their own ET. In all cases, the reason for referring the patients

Table 1: Patient demographics and characteristics

	Total (n=321)	Rejected IE (n=47)	Possible IE(n=34)	Definite IE (n=240)			P-value*
				Native valve (n= 125)	*Prosthesis (n=96)*	*Cardiac device (n=19)*	
Gender = Male, n(%)	228(71)	31(66)	25(74)		172(72)		0.69
				85(68)	*70(73)*	*17(89)*	0.15
Median Age (years)[IQR]	67 [55-77]	66 [57-75]	64 [55-74]		68[54-77]		0.69
				66[54-76]	*71[55-78]*	*66[61-75]*	0.34
Previous IE	21(7)	4(9)	4(12)		13(5)		0.33
				3(2)	*10(11)*	*0(0)*	0.02
CHD	34(11)	3(6)	5(15)		26(11)		0.45
				6(5)	*19(20)*	*1(5)*	0.001
History of Heart failure	36(11)	9(20)	7(21)		20(8)		0.02
				8(6)	*7(7)*	*5(26)*	0.01
Valve disease	172(54)	25(53)	18(53)		129(54)		0.99
				39(31)	*84(88)*	*5(26)*	<0.001
Cardiac device	70(22)	16(34)	14(41)		40(17)		0.001
				8(6)	*13(14)*	*19(100)*	<0.001
DM	59(18)	7(15)	8(24)		44(18)		0.59
				20(16)	*20(21)*	*4(21)*	0.60
Hypertension	96(30)	9(19)	11(32)		76(32)		0.19
				45(36)	*28(29)*	*3(16)*	0.17

IE: Infective endocarditis
CHD: Congenital heart disease
DM: Diabetes Mellitus
* P-value for the difference between rejected-, possible- and definite IE on the top of each box. The bottom p-value is the difference between native- prosthetic- and cardiac device IE for patients with the final diagnosis of definite IE.

was simply to adhere to the ESC guideline recommendations to refer all patients suspected for IE (included uncomplicated cases) to the ET. An overview of the baseline characteristics is presented in table 1.

Positive blood cultures were seen in 276/321(86%) patients, with *Staphylococcus aureus* (*S. aureus*) as the most common pathogen (n=76, 24%). An overview of the microbiological test results is presented in supplementary table S1.

Echocardiography was positive for IE in 206/321(64%) cases. The positive finding on echocardiography were vegetations (158/206, 77%), abscess (6/206, 3%), mycotic aneurysms/paravalvular leaks (9/206, 4%), new valvular insufficiency/stenosis (8/206, 4%) and combination of vegetations/abscess/(para)valvular insufficiency (25/206, 12%). PET/CT was performed in 152/321(47%) patients and was positive in 80/152(53%) patients. CTA was

Table 2: Diagnostic imaging performed

Imaging diagnostics	Total (n=321)	Rejected IE (n=47)	Possible IE (n=34)	Definite IE (n=240)			P-value*
				Native valve (n= 125)	*Prosthesis (n=96)*	*Devices (n=19)*	
Positive imaging n(%)	252 (79)	14(30)	16(47)		222(93)		<0.001
				118(94)	*88(92)*	*16(84)*	0.27
TTE/TEE performed n(%)	321 (100)	47(100)	34(100)		240(100)		NA
				125(100)	*96(100)*	*19(100)*	NA
Positive TTE/ TEE n(%)	206 (64)	8(17)	8(24)		190(79)		<0.001
				117(94)	*60(63)*	*13(68)*	<0.001
PET/CT performed n(%)	152 (47)	23(49)	18(53)		111(46)		0.74
				32(26)	*70(73)*	*9(47)*	<0.001
Positive PET/ CT n(%)	80 (25)	3(6)	7(21)		70 (29)		<0.001
				8(6)	*59(61)*	*3(16)*	<0.001
CTA performed n(%)	84 (26)	12(26)	10(29)		62(26)		0.90
				13(10)	*47(49)*	*2(11)*	<0.001
Positive CTA n(%)	63 (20)	5(11)	4(12)		54(23)		<0.001
				13(10)	*39(41)*	*2(11)*	0.23

IE: Infective endocarditis
TTE: Transthoracic echocardiogram; TEE: Trans oesophageal echocardiogram
PET/CT: positron emission tomography/Computed tomography
CTA: cardiac Computed tomography angiography
* P-value for the difference between rejected-, possible- and definite IE on the top of each box. The bottom p-value is the difference between native- prosthetic- and cardiac device IE for patients with the final diagnosis of definite IE.

performed in 84/321(26%) patients and was positive in 63/84(75%) patients. An overview of all diagnostic imaging results is presented in table 2.

The final diagnosis concluded by the ET was 47(15%) rejected, 34(11%) possible and 240(75%) definite IE with 125/240(52%) native valve IE, 96/240(40%) prosthetic valve IE and 19/240(8%) cardiac device-related IE. In 7/240(3%) patients, both a native and prosthetic valve (n=6) or prosthetic valve and a cardiac device (n=1) were involved. An overview of the results of all discussed patients is presented in figure 1.

Diagnostic and therapeutic impact

Additional microbiologic tests and imaging tests were advised by the ET in 69/321(21%) and 136/321(42%) cases, respectively. The reason for additional microbiologic tests were either initial negative or only one set of positive microbiologic tests in patients with high suspicion of IE. The results of these tests were negative in 21/69(30%) and positive in 48/69(70%) in patients. A change in diagnosis was observed in 53/321(17%) patients, out of which 39/53(74%) with reclassification from possible to rejected IE, 4/53(8%) from rejected

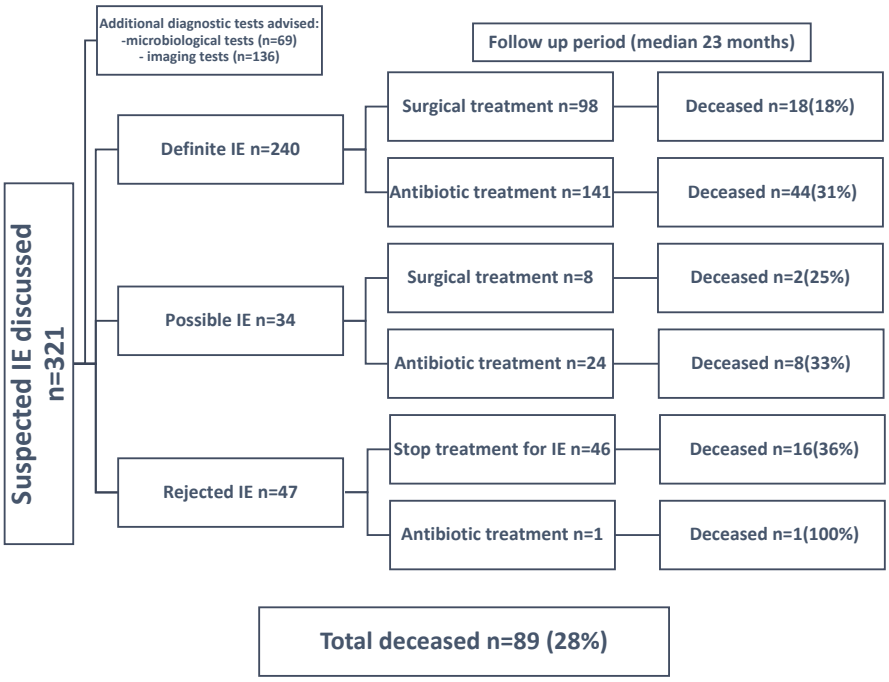

Figure 1: Overview of the results of 321 patients with suspected IE discussed in The Endocarditis team

to possible IE and 10/53(19%) from possible to definite IE. Reclassification was due to the advised additional diagnostic tests in 23/53(43%). In all other cases the reclassification was due to revision of patient data and the clinical images that were provided. Due to the advised additional diagnostic tests, there was a change in treatment in 31/321(10%) patients. In 16/321(5%) patients these changes were solely in antibiotic treatment and in 15/321(5%) the change was from a proposed conservative to a surgical management. Details per group are demonstrated in table 3.

Conservative and surgical treatment

An overview of the treatment policy for the total study population is presented in supplementary table S2. Antibiotic treatment only (without surgical intervention) was applied to 166/321(52%) (141 definite IE) patients as surgical intervention (alongside with antibiotic treatment) was needed in 107/321(33%) (98 definite IE) patients. Device extraction was performed in 16/20(80%) patients with definite cardiac device IE. No treatment advice was given to 48/321(15%) out of which 47 patients with rejected IE and 1 patient with possible IE who was already treated with antibiotic therapy for another infection and who showed no signs of active endocarditis at the moment of discussion.

Table 3: Additional diagnostic tests advised by the Endocarditis team

Additional diagnostic tests	Total (n=321)	Rejected IE (n=47)	Possible IE (n=34)	Definite IE (n=240)			P-value*
				Native Valve (n=125)	*Prosthesis (n=96)*	*Devices (n=19)*	
Micro-biological tests n(%)	69(21)	15(32)	10(29)		44(18)		0.06
				26(21)	*15(16)*	*3(16)*	0.60
Imaging tests n(%)	136(42)	17(36)	17(50)		102(43)		0.46
				49(39)	*49(51)*	*4(21)*	0.03
Diagnostic change due to additional diagnostic tests n(%)	23(7)	8(17)	2(6)		13(5)		0.02
				2(2)	*11(12)*	*0(0)*	0.01
Therapeutic change due to additional diagnostic tests n(%)	31(10)	5(11)	2(6)		24(10)		0.14
				10(8)	*14(15)*	*0(0)*	0.15
Change to invasive treatment due to additional microbiological tests n(%)	2(1)	0(0)	0(0)		2(1)		0.18
				1(1)	*1(0)*	*0(0)*	0.59
Change to invasive treatment due to additional imaging tests n(%)	13(4)	0(0)	1(3)		12(5)		0.05
				5(4)	*7(7)*	*0(0)*	0.35

IE: Infective endocarditis

* P-value for the difference between rejected-, possible- and definite IE on the top of each box.

The bottom p-value is the difference between native- prosthetic- and cardiac device IE for patients with the final diagnosis of definite IE.

Follow up

Two patients were lost to follow up due to moving to another country shortly after hospitalization.

During a median follow up period of 23[12-38] months the mortality rate for patients with the final diagnosis rejected, possible and definite IE was 17/47(36%), 10/34(29%) and 62/240(26%) respectively(p=0.08). For native valve IE, prosthesis IE and cardiac device-related IE the mortality rate was 25/125(20%), 32/96(33%) and 5/19(26%) respectively (p=0.78). The cause of death, could not always be derived from the follow up data. Figure 2 demonstrates the survival curves of every group.

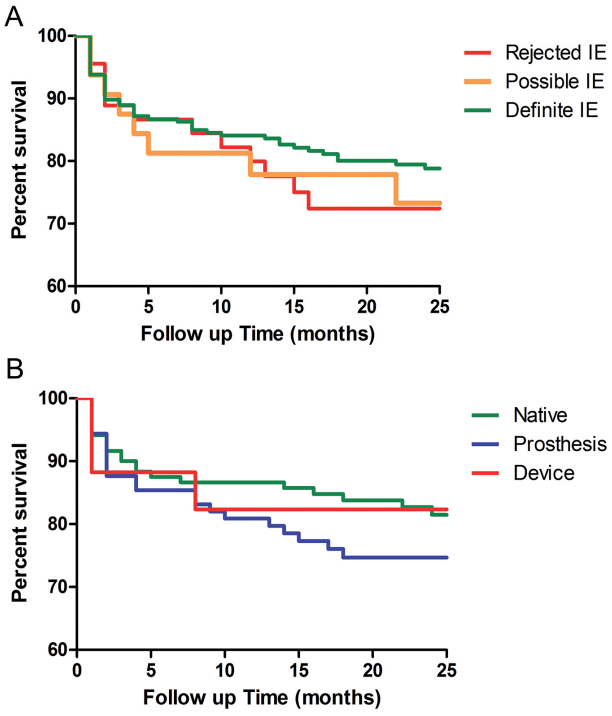

Figure 2: The survival curve of all discussed patients per group (A) and the patients with definite IE per category (B)

The 30-day mortality rate of patients who underwent surgical treatment was 8/107(7%), out of which 1 patient with elective surgery, 2 with device extraction and 5 with urgent surgery. The 30-day mortality rate of patients with definite cardiac device IE without device extraction was 1/4(25%).

The rate of relapse/re-infection during the follow up period was 10/240(4.2%) for the definite IE, out of which 4(1.7%) patients with relapse and 6(2.5%) patients with re-infection. For native valve IE, prosthesis IE and cardiac device-related IE the rates of relapse/re-infection were 2/125(1.6%), 8/96(8%) and 0/19(0%) respectively(p=0.03). The incidence rate for relapse/re-infection is shown in figure 3.

Discussion

The present study shows that ET provided a 17% change in diagnosis, 42% change in antibiotic treatment and 5% change from conservative to invasive treatment. This implies that a multidisciplinary approach results in a difference in policy in about half of the patients.

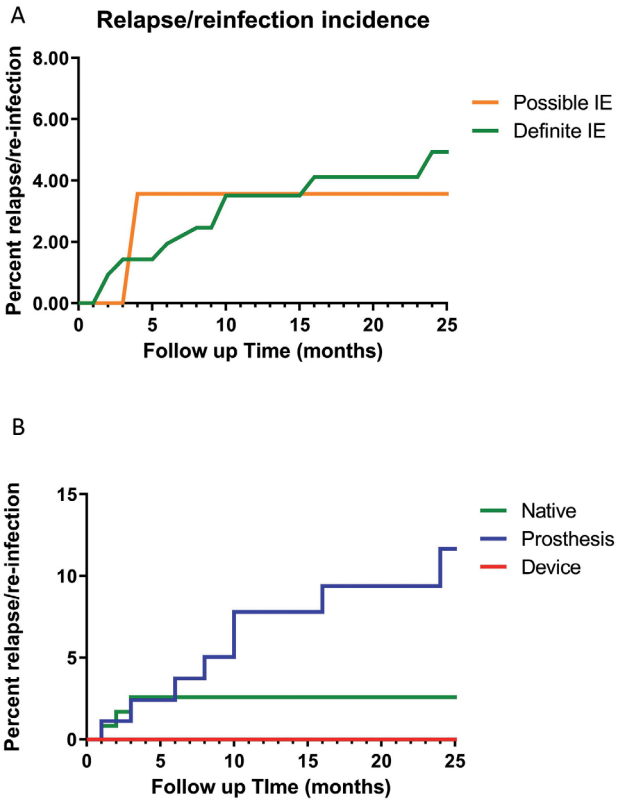

Figure 3: The incidence curve for relapse/re-infection of all patients with possible and definite IE (A) and patients with definite IE per category (B)

The difference of advice from the ET relative to the policy of the referring physician could be explained by the level of information that was available to the physicians of the ET compared to those from the referring hospitals. In some cases, the members of the ET had less information about the microbiological results, such as missing susceptibility values. In addition, in some cases the ET members had more information than to the referring physician, due to additional imaging diagnostic results that were revised by the ET. Another explanation could be that ET members had more experience in the treatment of specific patients with IE and were thus able to provide an expert opinion.

Additional advised diagnostic tests changed the diagnosis in only 23/321(7%) patients, and were primarily advised in order to rule out complications of IE. Although, this could be seen as a defensive strategy, it was according to the ESC guidelines and it did lead to a change in therapy in 31/321(10%) patients, that otherwise could have suffered from severe consequences.

The mortality rate in our study (28%) did not differ between rejected, possible and definite IE, nor did this differ between the native, prosthesis and cardiac device IE groups (figure 2). Compared to other studies that report an in-hospital mortality of 17% in the first 2 months after diagnosis and 27% in the first 6 months after diagnosis (5, 11), the mortality report in our study after a median follow up time of 23 months can be interpreted as mildly better. The mortality rate in our study could partially be explained by the possible referral bias, since complicated cases are more likely to be referred compared to uncomplicated cases or, the very severe cases with no hope for response to treatment can be left untreated and not be referred. The exact incidence number of patients with IE in the Netherlands is unknown. However, it could be presumed that this number is close to 45 patients per million inhabitants per year, which has also been described in other European countries (1). The region of our hospital has 1.58 million inhabitants which equals an incidence of 284 patients per 4 years. This number is slightly higher than the possible/definite IE cases in our study, which indicates that we have not included all patients from the region.

Multiple challenges can be encountered in the process of setting up an ET, such as determining and inviting the required specialists who should attend the meeting. Nowadays, imaging techniques such as PET/CT and CTA are advised to be used more often for the diagnosis of IE (1). In our opinion, the presence of a cardiac radiologist or cardiac imaging specialist during an ET discussion is important, since the recently introduced imaging techniques can sometimes be difficult to interpret in light of their limitations and technical aspects that need to be considered. Other challenging aspects of setting up an ET may be the timing and location of the meetings, the preparation of the cases and collection of all necessary information for a meaningful discussion. These challenges could be met by having a coordinator who keeps an overview of the cases that are needed to be discussed and who plays a key role in the management of these tasks. Furthermore, with digital communication solutions becoming more and more generally available in hospitals due to Corona virus disease 2019 pandemic, we also see opportunities for more interactive meetings with attending physicians from referring centres, which would not only provide more insight in the ET's considerations but could also serve an important educational role (12).

Our study has some limitations, such as the incapability of providing a true population-based sample of patients with IE. We relied on other referring centres for the number of patients discussed in our Endocarditis team. Furthermore, we also relied on the referring centres to provide a complete set of information, which was not always available. Another limitation is that it was not possible to verify whether the provided advice by the ET was adhered to by the referring physician. This may have influenced the follow-up outcomes of both mortality and relapse/re-infection rates.

In conclusion, the ET has a large impact on the policy of patients with suspected IE with a substantial change in diagnosis and treatment. Therefore, it should be implemented in all tertiary cardiothoracic centres and is optional for other hospitals.

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Table S1: Blood culture results

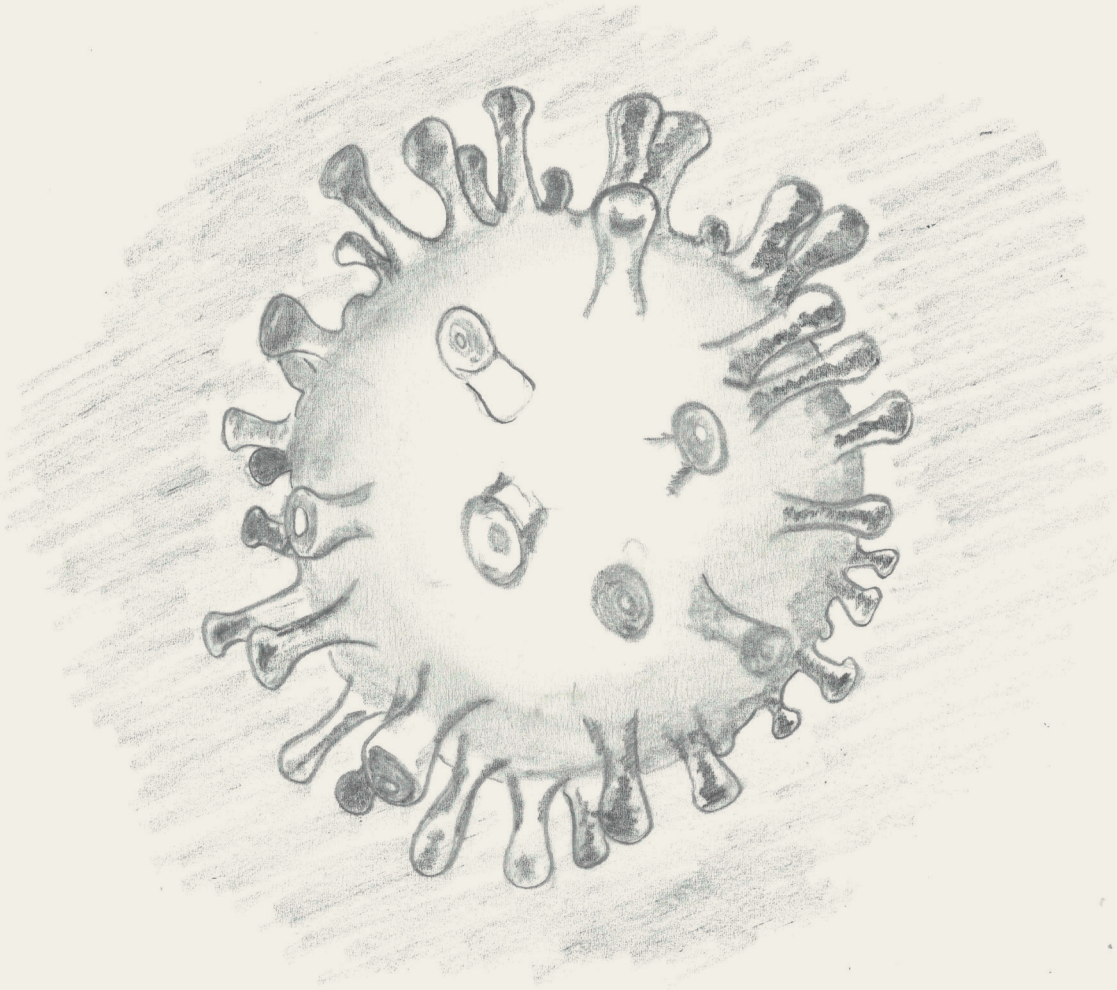
Blood cultures	Total (n=321)	Rejected IE (n=47)	Possible IE (n=34)	Definite IE (n=240)			P-value*
				Native valve (n= 125)	*Prosthesis (n=96)*	*Devices (n=19)*	
Positive BC, n (%)	276 (86)	28(60)	28(82)		220 (92)		<0.001
				116(93)	*86(90)*	*18(95)*	0.61
S. aureus* n (%)*	77 (24)	10(21)	11(32)		56(23)		0.46
				26(21)	*22(23)*	*8(42)*	0.12
***Other Staphylococci* n (%)**	24 (7)	5(11)	0(0)		19(8)		0.17
				9(7)	*7(7)*	*3(16)*	0.42
***Viridans group Streptococci* n (%)**	89(28)	9(19)	2(6)		78(33)		<0.01
				57(46)	*19(20)*	*2(11)*	<0.01
***Enterococcus faecalis* n (%)**	32 (10)	1(2)	7(21)		24(10)		0.02
				11(9)	*12(13)*	*1(5)*	0.51
***Enterococcus faecium* n(%)**	4(1)	0(0)	1(3)		3(1)		0.50
				2(2)	*1(1)*	*0(0)*	0.82
***Other Streptococci* n (%)**	18 (6)	3(6)	1(3)		14(6)		0.77
				6(5)	*7(7)*	*1(5)*	0.73
***Cutibacterium acnes* n (%)**	9 (3)	0(0)	1(3)		8(3)		0.45
				0(0)	*8(8)*	*0(0)*	<0.01
***HACEK* n (%)**	8 (2)	0(0)	0(0)		8(3)		0.25
				2(2)	*3(3)*	*3(16)*	0.01
Other micro-organisms* n(%)**	15 (5)	0(0)	5(15)		10(4)		0.01
				3(2)	*7(7)*	*0(0)*	0.13

IE: Infective endocarditis
BC: Blood Cultures
HACEK: *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella.*
* P-value for the difference between rejected-, possible- and definite IE on the top of each box. The bottom p-value is the difference between native- prosthetic- and cardiac device IE for patients with the final diagnosis of definite IE.
** One patient in this group had positive blood cultures for Methicillin-resistant Staphylococcus aureus (MRSA)
**Other micro-organisms: *Abiotrophia defectiva; Campylobacter fetus; Candida glabrata; Candida parapsilosis, Enterobacter cloacae; Fusobacterium necrophorum; Granulicatella adiacens; Klebsiella pneumonia; Lactobacillus rhamnosus; Lactococcus garvieae; Listeria monocytogenes; Moraxella catarrhalis; Morganella morganii*

Table S2: Treatment policy for IE

Imaging diagnostics	Total (n=321)	Rejected IE (n=47)	Possible IE (n=34)	Definite IE (n=240)			P-value*
				Native valve (n= 125)	*Prosthesis (n=96)*	*Devices (n=19)*	
Antibiotic treatment only (no intervention) n (%)	166(52)	1(2)	24(71)	141(59)			<0.01
				71(57)	*66(69)*	*4(21)*	<0.01
Surgical Intervention n(%)	107(33)	1(2)	8(24)	98(41)			<0.001
				53(42)	*30(31)*	*15(79)*	<0.01
Elective surgery n (%)	40(12)	0(0)	4(12)	36(15)			0.02
				25(20)	*11(5)*	*0(0)*	0.03
Urgent/ emergency surgery n (%)***	50(16)	1(2)**	2(6)	47(20)			<0.01
				28(22)	*19(20)*	*0(0)*	0.07
Device extraction n(%)***	18(6)	0(0)	2(6)	16(7)			0.19
				0(0)	*1(1)****	*15(79)*	<0.001
Change from conservative to invasive treatment advised by ET n(%)	15(5)	0(0)	1(3)	14(6)			0.2
				6(5)	*8(8)*	*0(0)*	0.29

IE: Infective endocarditis
ET: Endocarditis Team
*P-value for the difference between rejected-, possible- and definite IE on the top of each box. The bottom p-value is the difference between native- prosthetic- and cardiac device IE for patients with the final diagnosis of definite IE.
** One patient with rejected IE underwent an urgent valve surgery due to diagnosis of Libman Sacks endocarditis
***One patient underwent concomitant urgent surgery and device extraction for the diagnosis of both PVE and cardiac device-related IE.



Chapter 4

Heart Team Meetings during COVID-19

Different formats of multidisciplinary Heart Team Meetings under the Gathering Restriction Rules due to the Coronavirus Disease-2019 Pandemic are discussed

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Introduction

At the end of 2019, a novel strain of the coronavirus emerged in Wuhan, China and caused a respiratory infection named coronavirus disease 2019 (COVID-19)[1]. Due to the rapid worldwide spread of the virus the World Health Organisation (WHO) officially declared COVID-19 a pandemic on March 11, 2020[2]. In order to minimise the spread of the disease, many countries enacted precautionary measures, such as restrictions on gatherings and social distancing, following WHO guidelines[3].

In daily clinical practice, the coming together of physicians for multidisciplinary team (MDT) meetings is essential for good patient care. Examples in the cardiovascular field are Heart Team evaluations for coronary revascularization, valvular pathologies and Endocarditis, which have been recommended by the European Society of Cardiology (ESC).[4-6] Although these meetings are necessary and by definition not restricted, they could potentially increase the risk of spreading the virus, which should be prevented at all costs, specially between health care professionals. In order to continue to provide good patient care while minimising the risk of spreading the virus, other alternatives for conducting MDT meetings should be considered. In this article, we present four alternative methods (fig.1), along with their benefits and drawbacks (Table 1).

Alternative methods

Adjusted physical method

Presumably, physical meetings remain the most common method for physicians working in the same hospital to come together. However, these meetings should be adjusted to minimise viral transmission by avoiding any direct physical contact, restricting the number of participants and gathering in larger conference rooms. Before and after the meetings, participants should be reminded to sanitize their hands. Since the key characteristic of this method—the physical presence of the participants in the same area—remains unchanged and little effort is required from the participants, many physicians might prefer this approach during the COVID-19 pandemic. However, even if the risk of spreading the virus is relatively small, the risk still exists, and can be seen as a significant drawback.

Video conferencing

Video conferencing is an obvious alternative when physical meeting is not possible, with the benefit of eliminating the risk of viral spreading. Another advantage is the possibility to involve health care providers from other hospitals. However, there are a number of drawbacks, including connection issues, which could hamper communication and the loss of facial expression and body language, due to the often-limited resolution during a video

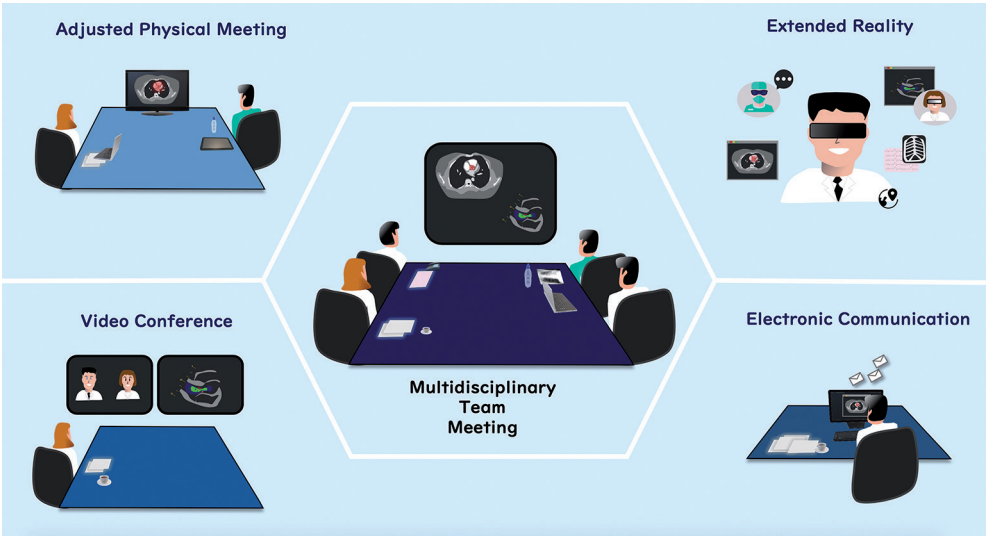

Figure 1: Four proposed alternative methods for the Heart Team meeting (A-D) with in the center the original form of discussion (E) in a virtual display

call. Other pitfalls may include the challenge of organising the meeting and preventing miscommunication, the need for secured software and finding a way for participants to watch the same screen as the presenter of the case.

Electronic communication

Another form of telemedicine is the use of electronic communication systems, such as electronic mail (e-mail) and the electronic health record (EHR). The proposed method could be achieved by communicating the designated case through EHR or e-mail with one person that coordinates the entire communication with all the participants. Using the EHR is preferable because it is usually a more secure data system than e-mail and the conclusion of the meeting is directly communicated to the attending physician. The benefits of this communication method are similar to those of video conferencing, with the addition of clearer communication since all participants are required to send a written response. However, a major drawback is the time-consuming nature of this type of communication, which is not desirable when decisions have to be made quickly. Needless to say, there is a loss of facial expression, tone and body language.

Extended Reality

Extended reality (XR) refers to all technologies that are used to create computer-generated digital three-dimensional interfaces that combine physical (real world) and virtual images that allow users to view and interact with both realities simultaneously.[7] XR interfaces can provide various types of human–machine interaction, including augmented reality (digital overlays on to the physically observed reality), virtual reality (fully digital/imagined virtual

Table 1: Benefits and drawbacks of the four alternative methods proposed for the Heart Team meetings

Methods	Benefits	Drawbacks
Adjusted physical meeting	Physical meeting with same setting Small effort to change	Remaining risk of infection or transmission of micro-organisms
Video Conference	No risk of infection or transmission of micro-organisms Possibility of participation for health care professionals from other hospitals	Connection problems Loss of non-verbal communication Organizing challenge to prevent miscommunication Need for secured software system Technical challenge in displaying the same desktop image to all participants
Electronic communication	No risk of infection Clearly written communication Conclusion of the meeting directly communicated to the attending physician	Time consuming Organizing challenge to prevent miscommunication Loss of non-verbal communication
Extended reality	No risk of infection Virtual interaction comparable with physical interaction	Still in development Not available for all health care professionals

world) and mixed reality (hybrid of virtual and digital worlds that is responsive to the user and real world).[8] Using wearables (e.g., remote controllers) and head-mounted devices (e.g., Microsoft Hololens, Oculus Rift), the user is able to view, engage and interact with these digital interfaces.[8,9]

Due to recent advances in the field of XR, virtual reality has found application in medical education and communication.[10,11] Regarding communication, there is a growing body of literature on the development of software and hardware platforms that offer communication facilitated by XR modalities.[12,13] These technologies enable teleconferencing and communication through the addition of new dimensions and features, such as video avatars, virtual rooms, animations and digital interaction.[12-14] There have been recent news reports on the use of XR in a telemedicine conference between three surgeons facilitated by a mixed reality interface.[15] The benefits of this method are similar to the video conferencing with the addition that the virtual interaction could be comparable with physical interaction.

However, the main question remains, whether these platforms are suitable for medical telecommunication purposes? In the context of medical televirtuality, platforms should preferably meet some strict security requirements to protect medical records and patient data. In addition, the hardware and software should be easy to use and allow interaction between physicians. With the recent and rapid developments in these emerging technologies,

it is vital to assume that the application of XR in medical televirtuality will become a reality in the near future.

Essential role of a coordinator

The coordinator should have the responsibility to gather all information needed for each meeting, invite the essential participants, explain the steps of the meeting and coordinate the meeting so it will be run smoothly. The role of a coordinator is essential in all of the proposed methods, especially in those that are prone to miscommunication.

Conclusion

To minimise the risks of transmission during the COVID-19 pandemic, alternative communication methods for MDT meetings, such as adjusted physical meetings, video conferencing, electronic communication and immersive telecommunication (extended reality), may be considered based on local needs and resources.

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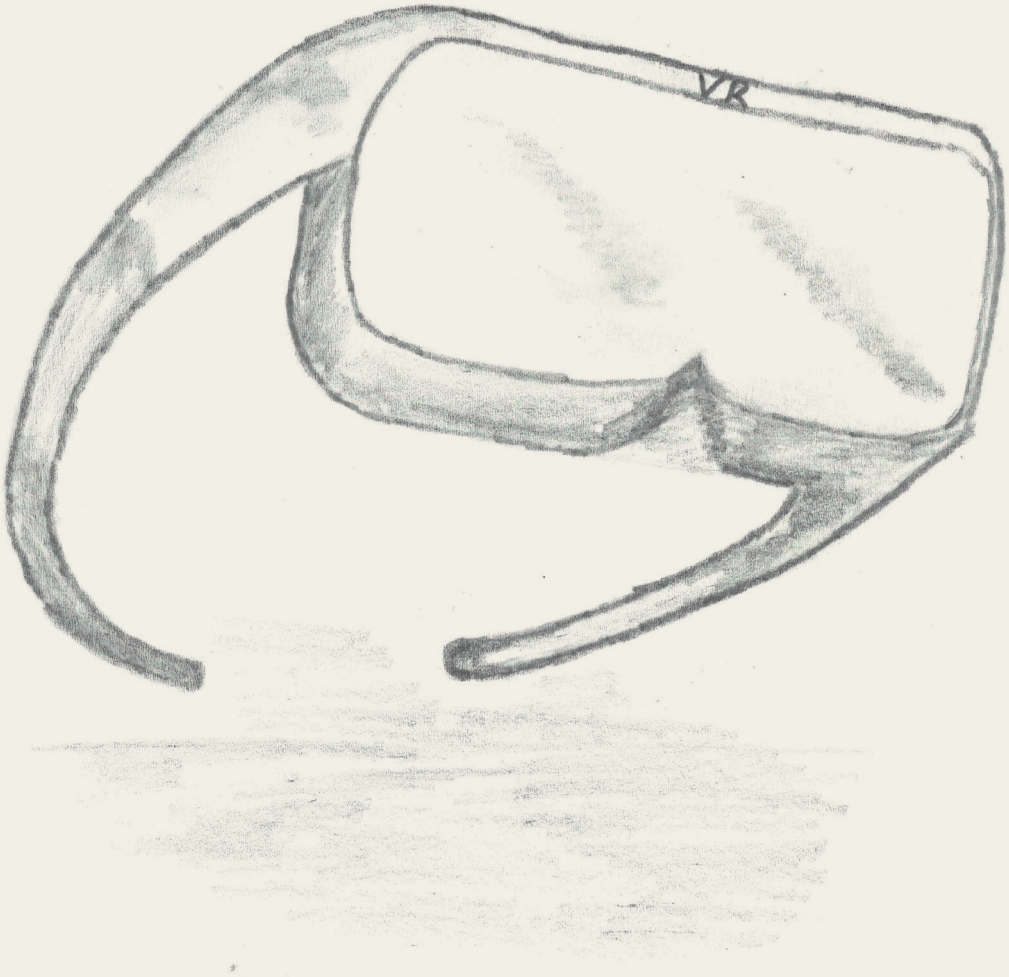
VR

Chapter 5

Remote multidisciplinary heart team meetings in immersive virtual reality: a first experience during the COVID-19 pandemic

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Abstract

Background: Due to the gathering restrictions in times of coronavirus disease 2019 (COVID-19) outbreak, alternative methods for multidisciplinary meetings need to be installed in order to provide good patient care. One of the alternative methods is the use of Virtual reality (VR), which has an increasing popularity in cardiovascular medicine However, no study on the organization of clinical multidisciplinary heart team meetings in VR is available. This observational proof-of-concept study aims to demonstrate the feasibility, effectiveness, and user experience of a VR-based multidisciplinary heart team meeting.

Methods: Experimental remote and immersive VR-based multidisciplinary coronary revascularization heart team meetings were simulated and attended by 10 medical specialists. After the meeting, a questionnaire was filled out by the participants, grading their VR-experience with different questions (ease-of-use, immersiveness (engagement), usefulness and effectiveness, and attitude towards (future) use).

Results: All VR-based multidisciplinary coronary revascularization meetings were organized successfully, and all the participants were independently unanimous about the therapeutical recommendation of the use case. “User-friendliness”, “safety”, “multidisciplinary and multi-user engagement in the conversation”, and “possibility to evaluate clinical imaging data” were the most common advantages mentioned by the participants in the questionnaire. Important disadvantages were the dependency on IT-infrastructure, the quality of the images, and the dependency and comfort of wearing VR-hardware.

Conclusions: VR can be used as an alternative method for remote conferencing in the setting of multidisciplinary team meetings for cardiologists and cardiothoracic surgeons and is specifically feasible during the gathering restriction rules of COVID-19 pandemic.

SUMMARY BOX

New Findings

- Due to COVID-19 pandemic, gathering restrictions have challenged the organization of physical multidisciplinary meetings, requiring innovative remote meeting methods, such as the immersive virtual reality-based method presented in this article.
- Immersive virtual reality-based coronary revascularization meetings were organized to enable remote multidisciplinary discussion between cardiac surgeons and cardiologists.

How does it impact on healthcare in the future?

- In the near future, extended reality platforms could overcome social distancing and gathering restrictions by enabling remote multidisciplinary collaboration for healthcare providers.
- Virtual reality-technology could have the potential to positively impact developments in pre-procedural medical planning, televirtuality, and digital health solutions that could benefit both patients and physicians.

Introduction

Virtual Reality (VR) is an emerging technology that enables creation of digital objects and virtual animations in a digital immersive environment that can be visualized and interacted with through head mounted displays (HMD) and controllers. [1 2] In the fields of cardiovascular medicine and surgery, an increasing number of reports have become available to demonstrate potential benefits of VR for education, surgical planning and simulation. [2-7] In addition, VR has made its entrance into the world of communication and is an ongoing topic of interest in scientific research and promising new tools are being developed. [8]

Due to the recent coronavirus disease 2019 (COVID-19) outbreak, local authorities have implemented several protective measures such as physical distancing and gathering restrictions. These restrictions have also been partly implemented in hospitals, however, in the fields of cardiology and cardiac surgery, full restrictions could potentially be harmful to patients, and therefore, alternative meeting methods should be implemented locally. Recently, we have published an article in which we present examples of alternative methods for multidisciplinary meetings to minimize the risk of viral infection and to ensure good and ongoing regular patient care. [8]

By combining VR meeting platforms with various HMD's, the user is able to immerse in a reality-like and fully 3D digital environment. VR-meeting platforms enable the users to get immersed in a virtual environment and provide them with digital tools (such as laser pointers and various meeting rooms) that enable VR-guided remote digital conferencing and televirtuality. By organizing remote multidisciplinary meetings, direct physical interaction can be avoided, and the risk of viral transmission can be minimized. Until now, no studies on the organization of clinical multidisciplinary heart team meetings in immersive VR are available in the literature. In order to study the feasibility, effectiveness, and user experience of a VR-based multidisciplinary heart team meeting, we have set up an observational proof-of-concept study, which was accelerated by the COVID-19 pandemic. Here, we describe our first experience on the application of VR meeting platforms in the setting of multidisciplinary coronary revascularization heart team meetings.

Methods

Experimental setup

At the Erasmus University Medical Center, a heart team meeting is held with at least an interventional cardiologist and a cardiothoracic surgeon. Five cardiothoracic surgeons (one in training) and five cardiologists were invited to participate in this study. Before the VR-meetings, all participants were briefed (5 min) on how to use the hardware and

software. Immersive VR-based remote multidisciplinary coronary revascularization heart team meetings were simulated according to local principles and with adherence to local gathering restriction rules (Figure 1). Each VR-meeting consisted of at least two participants from both cardiology and cardiothoracic surgery department. A total of 10 meetings were organized consisting of at least one study participant (cardiologist/cardiac surgeon) and one resident cardiology/cardiothoracic surgery physician. Participants remotely joined a virtual room in a VR-based meeting platform (MeetinVR, Copenhagen, Denmark) by using VR-1 (Varjo, Helsinki, Finland) and Rift S (Oculus, Irvine, California) HMD's, VR-controllers, and

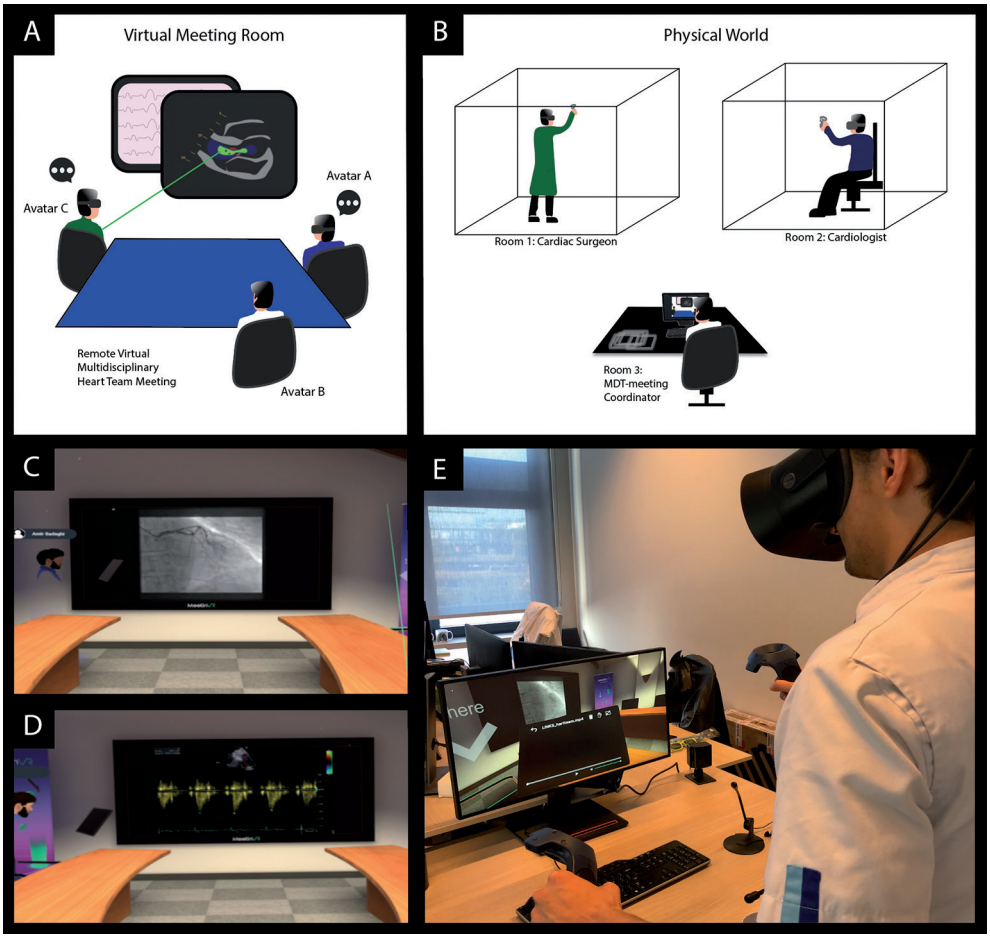

Figure 1. Immersive virtual reality based coronary revascularization heart team meetings

(A, B) Illustrative depiction of the experimental setup for remote multidisciplinary heart team meetings. Participants in remote areas of the hospital (right panel) joined a virtual meeting room as an avatar (left panel) and discussed a clinical case of a patient with coronary artery disease that was presented by an MDT-(multidisciplinary team meeting) coordinator.

(**C, D**) Several screenshots that have been acquired during a multidisciplinary remote and virtual reality-based heart team meeting. (**E**) In addition, photos present the hardware setup that enable remote virtual reality meetings

high-performance Thinkstation (Lenovo, Quarry Bay, Hong Kong) computers. Experienced VR-users were on site to provide technical support during the meetings. During the VR-meetings, a coordinator (resident physician) provided heart team participants anonymized medical images (coronary angiography, echocardiogram, electrocardiogram, and chest X-ray) of a patient with confirmed three-vessel coronary artery disease (history of hypertension, diabetes, and good left ventricular function) who already had been discussed in an earlier heart team meeting. The study was conducted in accordance with the principles of the Declaration of Helsinki and did not fall under the scope of the Medical Research Involving Human Subjects and was approved by the medical ethical committee of the Erasmus University Medical Center (MEC- 2020-0363). Informed consent was obtained from the patient. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Objectives and questionnaires

The objective of this proof-of-concept study was to evaluate the feasibility and efficacy (being able to assess a case in VR) of organizing remote VR-meetings to simulate heart team meetings. We defined feasibility as the ability to create a multidisciplinary meeting in VR to enable review of clinical imaging data remotely. Secondly, our aim was to study the subjective VR-experience and benefits of immersive meetings through questionnaires (supplementary file S1) focused on: ease-of-use, immersiveness (engagement), usefulness and effectiveness, attitude toward (future) use usefulness and effectiveness, and attitude toward (future) use. Questionnaires were created based on existing literature. [9-13] A total of 25 questions were created and a Likert rating scale was used with items rated between 1 to 5 (supplementary file S1). In addition, the final decision and recommendation of all virtual heart teams were documented and compared to the clinical recommendation of the physical meeting.

Data analysis

Data was analyzed by using Excel 2020 version 16.43 (Microsoft, Redmond, Washington). Categorical discrete data (Likert rating scales) are represented are represented as counts/ proportions.

Results

Participants

Nine participants were male, and one was female. Eight out of ten participants had at least five years of experience in physical heart team meetings on a weekly basis. Two had >3 years of experience for at least 1-2 times a month. Most study participants (n=6) did not have any

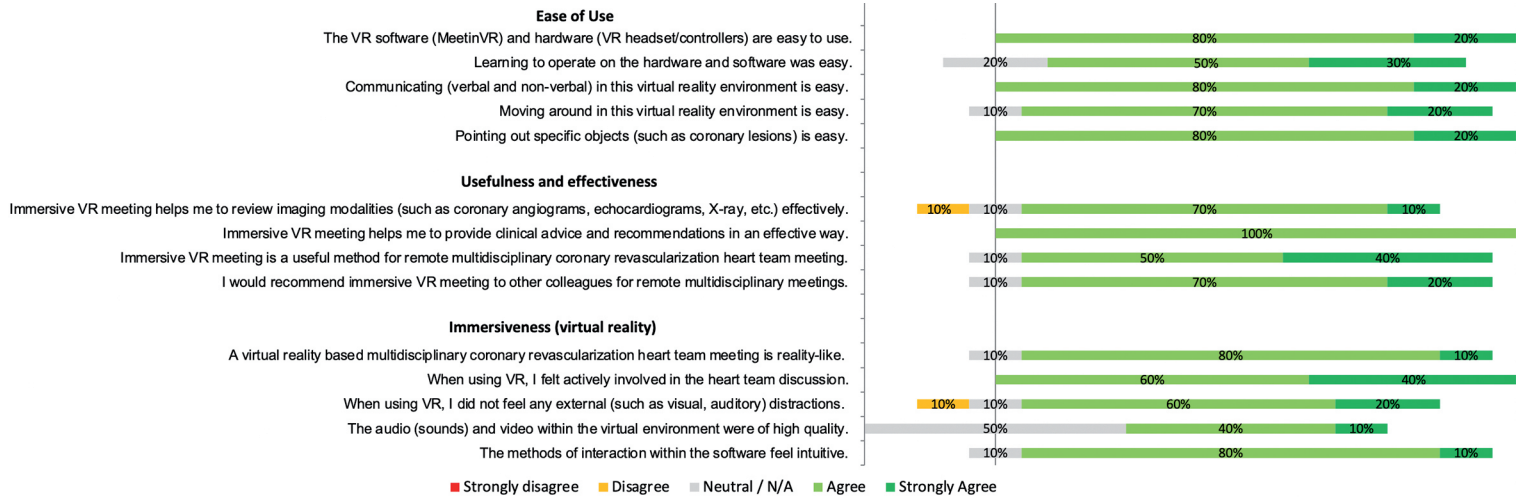

Figure 2. Questionnaire results on ease of use, usefulness and effectiveness, and immersiveness of virtual reality software and hardware for remote heart team meetings.

VR experience before, 3 had basic VR experience and 1 uses VR on a regular basis. None of the participants did have any experience in immersive VR-based remote meetings.

Feasibility

All VR-heart team meetings were organized successfully. All clinical imaging data were successfully visualized and assessed in VR (Figure 1). In all meetings, the team suggested coronary artery bypass grafting as the most suitable therapy. This corresponded with the clinical recommendation. The duration of the meetings was comparable to regular physical meetings with a maximum of 10 minutes (excluding 5 min of briefing).

Ease-of-use, immersiveness, usefulness, and effectiveness

An overview on the results of the questionnaires is presented in Figure 2. In general, VR-based meetings were rated as an easy-to-use, useful, and effective method for remote heart team meetings. The participants were also asked to fill out advantages and disadvantages of VR-based meetings. These results are presented in supplementary file S2. Some of the most common advantages were user-friendliness, safety, engagement (especially during social distancing) and pointing out specific lesions in VR by all participants. Important (potential) disadvantages were the dependency on IT-infrastructure, the quality of the images, and the dependency and comfort of wearing VR-hardware.

Alternative methods and future use

Ease-of-use, usefulness and effectiveness were rated to be better than tele/video conferencing by 90% of the users. Interestingly, when compared to physical meetings, 50% of the users rated VR-meetings to be similar and 20% rated VR-meetings to be much better. In addition, immersiveness was rated better when than tele/video conferencing by 90% of the users. Please refer to supplementary Figure 1 for a detailed overview of these results.

Ninety percent of the participants rated VR meetings to be a good method for future remote meetings and would like to work with this technology in the future and 80% of the users thought that in the future, they would even prefer working with this technology rather than tele/video conferencing. However, when compared to physical meetings, 50% did not prefer VR. See supplementary Figure 2 for a detailed overview.

Discussion

In this study we present the first examination of VR-based remote multidisciplinary heart team meetings to overcome social distancing challenges due to COVID-19. Remote meetings were organized in immersive VR using head mounted displays and controllers and by providing a clinical case of a patient with coronary disease. We found that in general, the

user experience was rated positive and that there was a positive attitude towards the use of VR as an alternative method for remote conferencing. An appreciated feature was found to be the possibility interact and to point out lesions directly with a virtual laser-pointer. This seemed to be an important shortcoming of 2D tele/video conferencing methods, where only one user can point out lesions (with a mouse arrow) when he/she is actually sharing his/her screen. Another advantage that was mentioned frequently was the engagement in the meeting. Due to all immersive features, the participants felt actively involved in the meetings and did not experience visual or auditory distractions from their surroundings. In addition, communication was mentioned to be intuitive and as good as a physical meeting, which underlines the advantages of immersive VR even more. Based on the questionnaire results and the experiences, it seems of the utmost importance that a VR device should be easy to use, light in weight, applicable to different types of software, and preferably unwired. In addition, it should be possible to wear the headset when wearing glasses. For future clinical implementation, it is important to design a highly secured platform which is connected to the electronic health record, so a large set of patient data can be uploaded without any delay or inefficient anonymization procedures. Moreover, a platform is needed that offers high security and compliance standards. For regular clinical implementation during a pandemic, hygienic measures should be taken into account as well. Even though most participants were excited using this novel VR technology, also some shortcomings and disadvantages were mentioned. For example, there seemed to be quite some room for improvement in terms of image quality. In some cases, the pixels on the shared monitor in the virtual meeting room were visible and thus the angiography images seemed to be a little less clear. However, most participants (80%) did not feel that this resulted in a less effective assessment of imaging modalities. (Figure 2)

With regard to the future, an interesting application of immersive technology and televirtuality would be the possibility of a real-time and remote evaluation of a patient through holographic telepresence and mixed reality technology. [14] Finance is another important factor in considering structural clinical implementation and therefore a cost-effectiveness study would be desirable. A recent review on the use of telemedicine for multidisciplinary meetings demonstrated that some of the important advantages that telemedicine has to offer are decreased burdens of travel, a reduction of travel expenses, and a reduction of overtime. [15] Lack of acceptance associated costs of technology and suboptimal availability of an IT-infrastructure were identified as possible challenges and barriers for implementation of telemedicine for multidisciplinary meetings.

Besides enabling remote multidisciplinary meetings, VR technology has the potential to result in further advances in medicine and could be beneficial for both patients and physicians. Specifically, during these challenging times, alternative simulation and communication methods can be beneficial for physicians to cope with the current restriction rules due to

COVID-19 but might also be a valid option for the future. [16 17] More development, research and validation in technology could hopefully pave the way for a fully remote and immersive experience for the future of clinical medicine. Finally, we believe that future studies, comprising several cases and larger datasets that directly compare VR-based methods to other alternatives (e.g., tele/video conferencing) are needed to draw conclusions.

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Supplementary file S1

Immersive virtual reality coronary revascularization heart team meeting questionnaire

How often do you participate in coronary revascularization heart team meetings?

1. I never participate in coronary revascularization heart team meetings
2. I participate incidentally (less than once per month) in coronary revascularization heart team meetings
3. I participate sometimes (1-2 times / month) in coronary revascularization heart team meetings
4. I participate often (every week) in coronary revascularization heart team meetings

How many years of experience do you have in participating in coronary revascularization heart team meetings?

1. I have 0-1 years of experience in participating in coronary revascularization heart team meetings
2. I have 1-3 years of experience in participating in coronary revascularization heart team meetings.
3. I have 3-5 years of experience in participating in coronary revascularization heart team meetings.
4. I have >5 years of experience in participating in coronary revascularization heart team meetings.

How often do you use Virtual Reality hardware/software (e.g. virtual reality gaming, virtual reality simulations, virtual reality consoles, etc.)?

1. I have no experience (I never had VR experience until today)
2. I have basic experience (I have had some incidental VR experiences before, e.g. gaming, entertainment, etc.)
3. I am experienced (I use VR consoles and applications on a regular basis).
4. I am an expert (I have a VR console and applications myself).

Do you have any experience in immersive (virtual reality-based) remote meetings?

1. Yes
2. No

Ease of Use

1. The VR software (MeetinVR) and hardware (VR headset/controllers) are easy to use.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

2. Learning to operate on the hardware and software was easy.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

3. Communicating (verbal and non-verbal) in this virtual reality environment is easy.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

4. Moving around in this virtual reality environment is easy.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

5. Pointing out specific objects (such as coronary lesions) is easy.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

Usefulness and effectiveness

1. Immersive VR meeting helps me to review imaging modalities (such as coronary angiograms, echocardiograms, X-ray, etc.) effectively.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

2. Immersive VR meeting helps me to provide clinical advice and recommendations in an effective way.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

3. Immersive VR meeting is a useful method for remote multidisciplinary coronary revascularization heart team meeting.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

4. I would recommend immersive VR meeting to other colleagues for remote multidisciplinary meetings.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

Immersiveness (virtual reality)

1. A virtual reality based multidisciplinary coronary revascularization heart team meeting is reality-like.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

2. When using VR, I felt actively involved in the heart team discussion.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

3. When using VR, I did not feel any external (such as visual, auditory) distractions.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

4. The audio (sounds) and video within the virtual environment were of high quality.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

5. The methods of interaction within the software feel intuitive.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

Alternative meeting methods

1. Regarding ease-of-use, **virtual reality** conferencing is a…….. way for organizing remote heart team meetings when compared to **tele/video** conferencing.

5 Much Better	4 Somewhat better	3 Similar	2 Somewhat worse	1 Much Worse

2. Regarding usefulness and effectiveness, **virtual reality** conferencing is a…… way for organizing remote multidisciplinary heart team meetings when compared to **tele/video** conferencing.

5 Much Better	4 Somewhat better	3 Similar	2 Somewhat worse	1 Much Worse

3. Regarding usefulness and effectiveness, **virtual reality** conferencing is a…… way for organizing remote multidisciplinary heart team meetings when compared to **physical meetings**.

5 Much Better	4 Somewhat better	3 Similar	2 Somewhat worse	1 Much Worse

4. Regarding immersiveness (engagement in virtual environment), **virtual reality** conferencing is a…… way for organizing remote multidisciplinary heart team meetings when compared to **tele/video** conferencing.

5 Much Better	4 Somewhat better	3 Similar	2 Somewhat worse	1 Much Worse

Attitude towards (future) use

1. VR meetings are a good method for future remote coronary revascularization heart team meetings.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

2. I would like to work with this technology in the future.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

3. I enjoyed using VR for remote multidisciplinary meetings.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

4. In the future, I prefer using virtual reality conferencing methods over **tele/video** conferencing methods.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

5. In the future, I prefer using virtual reality conferencing methods over **physical** conferencing methods.

5 Strongly Agree	4 Agree	3 Neither Or N/A	2 Disagree	1 Strongly Disagree

Please provide advantages and disadvantages of immersive VR technology for organizing multidisciplinary meetings (please rank in order of importance *(start with the most important (dis)advantages)*

Advantages:

1. …….
2. …….
3. …….

Disadvantages:

1. …….
2. …….
3. …….

Did you feel that there were missing features in this virtual reality environment?

…..

Thank you for your participation

Supplementary file S2

Participant's opinion on advantages and disadvantages of remote multidisciplinary coronary revascularization heart team meetings in virtual reality.

Participant 1
Advantages:
1. Avoidance of distraction from surroundings.
2. Clear audiovisual content.
3. Attractive virtual meeting room.

Disadvantages:
1. Wearing glasses.
2. Sharpening the images for participants.
3. Costs?

Participant 2
Advantages:
1. No need to travel.
2. Decrease the risk of infection during COVID-19 pandemic.

Disadvantages:
1. Quality of the videos.

Participant 3
Advantages: none.
Disadvantages: none.

Participant 4
Advantages:
1. Could be of great help to organize "physical-like" meetings to meet colleagues in other/remote hospitals.

Disadvantages:
1. None.

Participant 5
Advantages:
1. Ease of use.
2. Good visualization of angiography/chest X-ray of patient.
3. Good communication.

Disadvantages:
1. Dependent upon internet.

Participant 6
Advantages:
1. Great method to engage in the heart team discussions (or other meetings) requiring participants interaction with the data showed (in this case angio and echo). This is not quite possible with video/teleconferences.
2. Best option for remote meetings during these pandemic times.
3. Good sound and user friendly.

Disadvantages:
1. It requires to be in possession of a VR equipment (somehow expensive?).
2. As an alternative to physical meetings during the pandemic it might mandate specific protocols for use in order to keep the risk of virus transference between users low.
3. Some people might not tolerate the virtual reality environment and might feel nausea or dizziness.

Participant 7
Advantages:
1. Distance is not a burden anymore.
2. Integration of images, also 3D/VR is possible.
3. It was OK when more people speak together.

Disadvantages:
1. Wearing VR glasses is awful compared to watch a screen!
2. Even more dependent on IT infrastructures and stability of networks.

Participant 8
Advantages:
1. Intuitive way of communication.
2. Pointing out lesions is doable in VR, but not in zoom/teams (video conferencing).
3. Fully immersive, less distraction from surroundings.

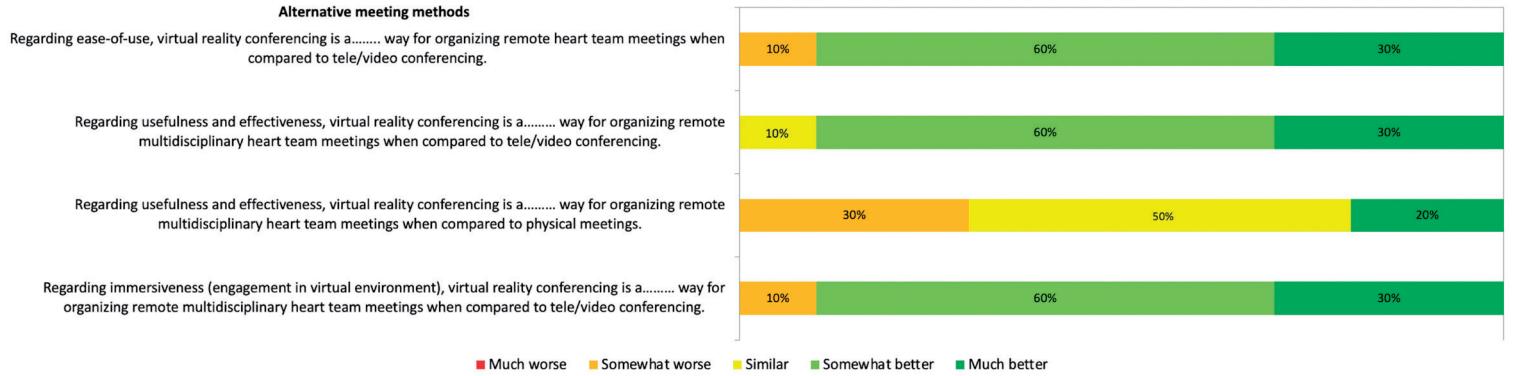
Disadvantages:
1. Quality of images (pixels can be seen).
2. Somewhat time-intensive to set up everything (in this proof of concept setup at least).
3. Delay in connection sometimes.

Participant 9
Advantages:
1. Direct contact with meeting participants.
2. Viewing images together with the possibility to interact.

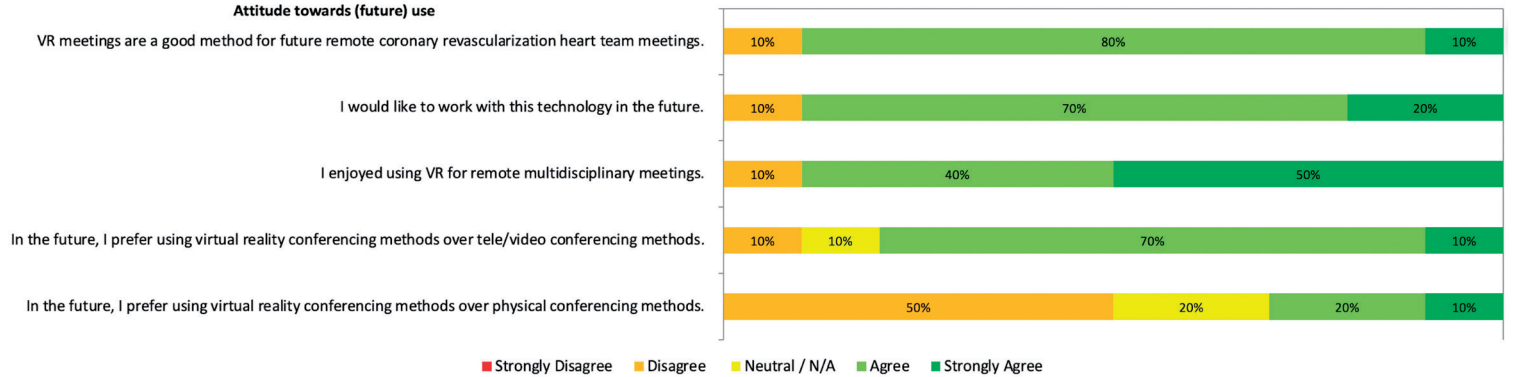
Disadvantages:
1. The above may not necessarily require VR; online communication and sharing images can also be done with other methods.
2. Image quality of coronary angiogram was suboptimal.
3. We would need methods to view images in original quality. In fact, this is more important than the way of communication.

Participant 10
Advantages:
1. No travel time.
2. As good as physical meeting.
3. Use of pointer by all the participants.

Disadvantages:
1. No sharp images
2. Learning curve to handle tool.



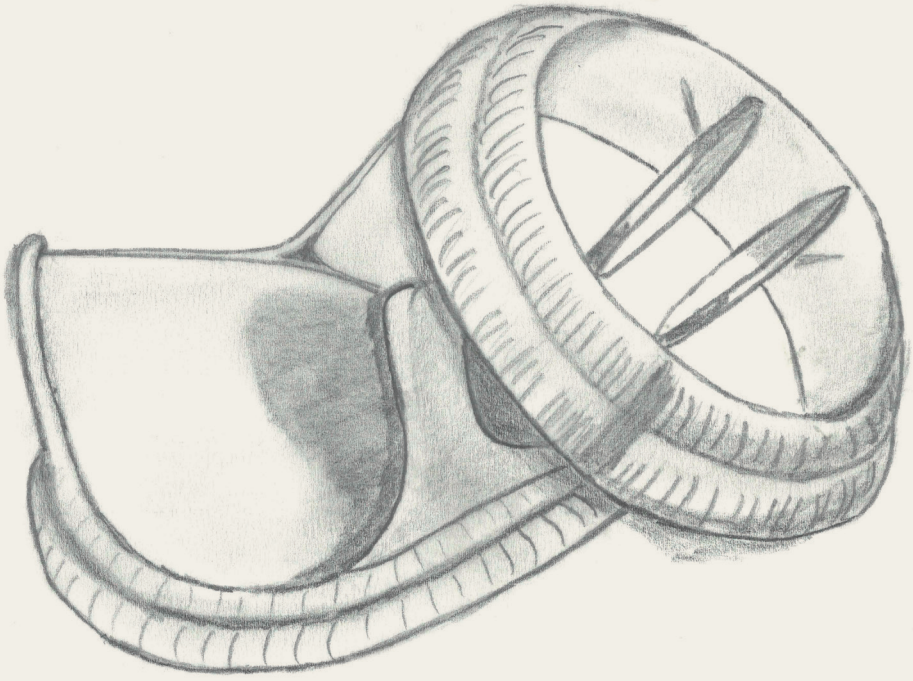
Supplementary figure 1



Supplementary figure 2

PART III

The Value of PET/CT in the Diagnosis of Infective Endocarditis



Chapter 6

Normal Imaging Findings after Aortic Valve Implantation on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography with Computed Tomography

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Abstract

Background: To determine the normal perivalvular ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) uptake on Positron Emission Tomography (PET) with computed tomography (CT) within one year after aortic prosthetic heart valve (PHV) implantation.

Methods: Patients with uncomplicated aortic PHV implantation were prospectively included and underwent ^{18}F-FDG PET/CT at either 5(±1) weeks (group 1), 12(±2) weeks (group 2) or 52(±8) weeks (group 3) after implantation. ^{18}F-FDG uptake around the PHV was scored qualitatively (none/low/intermediate/high) and quantitatively by measuring the maximum Standardized Uptake Value (SUV_{max}) and target to background ratio (SUV_{ratio}).

Results: In total, 37 patients (group 1: n=12, group 2: n=12, group 3: n=13) (mean age 66±8 years) were prospectively included. Perivalvular ^{18}F-FDG uptake was low (8/12(67%)) and intermediate (4/12(33%)) in group 1, low (7/12(58%)) and intermediate (5/12(42%)) in group 2 and low (8/13(62%)) and intermediate (5/13(38%)) in group 3 (p=0.91). SUV_{max} was 4.1±0.7, 4.6±0.9 and 3.8±0.7 (mean±SD,p=0.08), and SUV_{ratio} was 2.0[1.9-2.2], 2.0[1.8-2.6] and 1.9[1.7-2.0] (median[IQR],p=0.81) for groups 1, 2 and 3, respectively.

Conclusion: Non-infected aortic PHV have similar low to intermediate perivalvular ^{18}F-FDG uptake with similar SUV_{max} and SUV_{ratio} at 5, 12 and 52 weeks after implantation

Introduction

Diagnosing prosthetic heart valve (PHV) endocarditis remains difficult (1, 2). ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography (PET) with computed tomography (CT) was added as an additional diagnostic tool in the 2015 European Society of Cardiology (ESC) guidelines for infectious endocarditis (2). Since then, ^{18}F-FDG PET/CT has shown great potential for diagnosing PHV endocarditis, with a good sensitivity and specificity (3-5). For accurate interpretation of ^{18}F-FDG PET/CT scans in PHV patients suspected for endocarditis, knowing the normal amount and pattern of ^{18}F-FDG uptake around PHV's (due to the normal tissue healing response) is important. The ESC guidelines suggest using ^{18}F-FDG PET/CT only if the PHV was implanted >3 months prior to the scan because it was assumed that the normal healing response after aortic PHV implantation and its associated ^{18}F-FDG uptake would cause false positive results and misinterpretations within this time window (2). However, this arbitrary time period is not based on any evidence and has recently been questioned in other studies (3, 6). Indications of the normal ^{18}F-FDG uptake patterns and cut off values for abnormal uptake have been obtained from retrospective assessment of a limited number of patients with a PHV who underwent ^{18}F-FDG PET/CT for indications other than suspected endocarditis (3, 7). Recently, the first prospective study regarding baseline assessment of normal ^{18}F-FDG uptake patterns around PHV's was published showing no significant differences between ^{18}F-FDG uptake around PHV's at 1, 6 and 12 months after surgery (8). In this study, we prospectively assessed the qualitative and quantitative baseline perivalvular ^{18}F-FDG uptake at three different time points within the first year following aortic PHV implantation, in order to obtain normal ^{18}F-FDG uptake reference values.

Materials and methods

Patient selection and classification

In this prospective multi-center cross-sectional study, we included patients (age ≥50 years) from 2 different hospitals in the Netherlands (Erasmus Medical Center, Rotterdam, and the University Medical Center, Utrecht) who had undergone an uncomplicated aortic PHV implantation. An uncomplicated PHV implantation was defined as a PHV implantation without any surgical complication during or after the operation as well as the absence of signs of infection as mentioned in the surgical reports and the electronic patient files. The inclusion and exclusion criteria are detailed in table 1. The medical ethics committee approved the study (NL42743.041.12). All patients provided written informed consent.

Patients were divided into 3 groups and received an ^{18}F-FDG PET/CT at either 5(±1) weeks (group 1), 12(±2) weeks (group 2) or 52(±8) weeks (group 3) following valve implantation. The assignment of patients to each group depended on logistic factors such as availability of

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 50 years • Patients after uncomplicated PHV implantation in aortic position (mechanical and biological PHVs) • Normal routine follow up TTE (standardly performed 5 days after operation) or intra-operative TEE. With no signs of obstruction, endocarditis or significant paravalvular leakages. • Weight < 110 kg	• Known contrast allergy • Known renal impairment (according to local hospital guidelines) • Diabetes Mellitus • Mild contractile dysfunction of the left and/or right ventricle (Eyeballing, Ejection fraction <45 %, TAPSE <14 mm) • Active cardiac decompensation • Uncontrolled cardiac arrhythmias • Suspicion of active endocarditis • Previous participation in scientific studies using radiation. • (Possible) pregnancy in pre-menopausal women above 50 years not on reliable birth control therapy. Other contraindications for contrast use according to the standard daily clinical routine according to the protocol by the department of radiology • Use of pericardial patches and re-operation of aortic PHV in past medical history • Contraindication for Computed Tomography Angiography according the standard daily clinical routine • Refusal to be informed about potential additional CT or FDG-PET findings • If already included in group 1, patients cannot be included in group 2 or 3

PHV= Prosthetic heart valve
TTE= Transthoracic echocardiogram
TEE= Transesophageal echocardiogram
TAPSE= Tricuspid annular plane systolic excursion
CT= Computed tomography
FDG-PET= Fluorodeoxyglucose-Positron emission tomography

time slots on the PET/CT scanner and patient availability of one of the three time intervals after surgery.

Included patients had undergone uncomplicated valve implantations and did not have any clinical signs of prosthetic valve infection (fever, shivers, dyspnea, etc) at the time of the ^{18}F-FDG PET/CT.

Image acquisition

^{18}F-FDG PET/CT

To induce free fatty acid metabolism and suppress myocardial glucose metabolism, patients followed a 24-hour low carbohydrate diet, of which the last 12 hours were spent fasting (9-11). Thereafter, patients received an intravenous ^{18}F-FDG-injection of 2.0 MBq/kg. Patients were hydrated with 1000 ml of water 1 hour prior to image acquisition. Blood glucose levels

were checked before ^{18}F-FDG injection and the limit was set to 8.9 mmol/l. Approximately 1 hour after ^{18}F-FDG injection, the PET/CT was performed using a Biography Sensation 16scanner (SIEMENS Medical, Germany). Before the PET acquisition, a low dose CT-scan was performed for attenuation correction. A PET-scan of the heart was then obtained with 3-minute acquisitions per bed position using a 3-dimensional acquisition mode. Attenuation corrected PET images were reconstructed with an ordered-subset expectation-maximization iterative reconstruction algorithm.

Image analysis and interpretation

18F-FDG PET/CT analysis

Uptake of ^{18}F-FDG around the PHV was scored both qualitatively and quantitatively by an experienced nuclear medicine physician. For qualitative analyses, the Qualification Visual Score for Hypermetabolism (QVSH) was used, scoring the uptake as "none" (no or less than mediastinal uptake), "low" (more than mediastinal uptake but less than in the liver), "intermediate" (more than liver uptake), or "high" (intense uptake). Mediastinal uptake was defined as the mean uptake in the blood pool of the descending aorta at the level of the left atrium. Additionally, the location (former left coronary cusp (LCC)/right coronary cusp (RCC)/ non coronary cusp (NCC), circular, PHV struts only or ascending aorta) of this uptake was specified. Quantitative analyses were performed by measuring the maximum Standardized Uptake Value (SUV_{max}) and target to background ratio (SUV_{ratio}) on standardized European Association of Nuclear Medicine Research Ltd. (EARL) and non-EARL reconstructions using commercially available software (OsiriX MD version 7.5, Switzerland). SUV_{max} was measured in an automated volume of interest (VOI) around the PHV, which was visually verified to include the whole valve region. The SUV_{ratio} was then calculated as the ratio of the SUV_{max} and the mean SUV in the blood pool of the descending aorta, taking care not to include the vessel wall.

Myocardial suppression was scored as "fully suppressed" (no uptake), "low" (more than mediastinal uptake but less than in the liver), "intermediate" (more than liver uptake), "high focal" (much more than liver uptake, but focal), "high diffuse" (much more than liver uptake, diffuse).

Statistics

Descriptive statistics were used for analysis of the outcomes. For continuous variables, means and standard deviations (SD) were used in case of normal distribution. In case of non-normal distribution, medians and interquartile ranges (IQR) were used. The IQR and confidence interval (CI) were denoted in square brackets. Comparisons between groups were made using the Chi-square test for categorical variables. For continuous variables One-way Analysis of Variance (ANOVA) was used in case of normal distribution and Kruskal Wallis

test in case of non-normal distribution. A significance level of p=0.05 and 95% confidence intervals (CI) were used.

Results

Patients' characteristics and classification

A total of 38 patients were initially included after signing written informed consent. One patient was excluded after failure to undergo the PET/CT scan due to scanner malfunction. Age (mean±SD) of the 37 patients finally included in this study was 66±8 years (group 1: 65±7; group 2: 66±8; group 3: 67±10; p=0.87) and most of the patients were male (n=24, 65%) (group 1: n=8; group 2: n=10; group 3: n=6; p=0.15). There were 25 (68%) biological and 12 (32%) mechanical prosthetic valves, equally distributed between groups (p=0.99). Surgical adhesives such as BioGlue that are known to be FDG-avid, were not used during any of the implantations. No patient was suspected of having endocarditis prior to the PET/CT scan. Patients were included in either group 1 (n=12), group 2 (n=12) or group 3 (n=13). Due to logistic problems, 8 patients (group 1: n=2; group 2 n=3; group 3: n=3) underwent the scan outside the time interval originally set-out for each group. The 2 patients in group 1 were scanned 2 and 5 days later than the maximum adjusted days (5±1 week) for group 1. The 3 patients in group 2 were scanned 15, 22 and 38 days later and the 3 patients in group 3 were scanned 15, 23 and 36 days later than originally planned. Baseline characteristics for the overall population and the three groups are summarized in table 2.

^{18}F-FDG PET/CT findings

The median time between PHV implantation and ^{18}F-FDG PET/CT was 37 [IQR 35-42], 93 [IQR 87-109] and 370 [IQR 356-430] days for group 1, 2 and 3 respectively (p<0.01). Median ^{18}F-FDG dosage was 166 [IQR 145-183] MBq and not significantly different between the groups (p=0.16). Preparation according to carbohydrate diet protocol was followed by 36/37 (97%) patients. Three patients had fasted less than 12 hours prior to the scan, 1 patient failed to follow the low carbohydrate diet and 1 patient inadvertently received a double amount of ^{18}F-FDG activity. Myocardial ^{18}F-FDG uptake was scored as "fully suppressed" in 18/37 (49%) and as intermediate or less in 29/37 (78%) patients. One patient was scored as focal high and 7 patients as diffuse high myocardial uptake. The interpretation of one scan was hampered due to the diffuse high myocardial FDG uptake.

The QVSH around the PHV was scored as follows for group 1: low in 8/12 (67%) and intermediate in 4/12 (33%) patients; group 2: 7/12 (58%) low and 5/12 (42%) intermediate and for group 3: 8/13 (62%) low and 5/13 (38%) intermediate. Comparison between groups showed no significant difference in QVSH (p=0.91). The distribution of ^{18}F-FDG uptake was circular in most cases (78%) and not significantly different between the 3 groups (p=0.50).

Table 2: baseline characteristics of all patients and of patients in groups 1, 2 and 3

	All included patients	Group 1 (5 (±1) weeks after PHV implantation)	Group 2 (12 (±2) week after PHV implantation)	Group 3 (12 (±2) months after PHV implantation)	P-value***
Number of patients	37	12	12	13	
Age, mean±SD, years	66±8	65±7	66±8	67±10	0.87
Gender, n(%)					0.15
Male	24(65)	8(67)	10(83)	6(46)	
Female	13(35)	4(33)	2(17)	7(54)	
BMI, median [IQR], kg/m^2	27 [24-29]	26 [23-30]	26 [25-28]	28 [25-30]	0.60
Days between PET/CT and PHV implantation, median [IQR], days	94 [42-360]	37 [35-42]	93 [87-109]	370 [356-430]	<0.01
Laboratory results*					
Serum levels of leucocytes x10^9 /L, mean±SD	10.1±2.3	9.8±1.7	10.0±2.3	10.5±2.7	0.73
Serum levels of creatinine µmol/L, mean±SD	71±14	72±16	76±11	65±13	0.13
Serum levels of glucose mmol/L, mean±SD	5.4±0.7	5.5±0.6	5.5±0.8	5.2±0.8	0.46
Medical History, n(%)					
Hypertension	17(46)	6(50)	5(42)	6(46)	0.92
Atrial fibrillation	9(24)	2(17)	1(8)	6(46)	0.07
Heart failure	1(3)	0(0)	1(8)	0(0)	0.34
Myocardial infarction	1(3)	0(0)	0(0)	1(8)	0.39
Prior thoracic surgery	3(8)	1(8)	1(8)	1(8)	0.999
PHV type, n(%)					0.99
Mechanical	12(32)	4(33)	4(33)	4(31)	
Biological	25(68)	8(67)	8(67)	9(69)	
Valve manufacturer, n(%)					0.62
St. Jude	9(24)	3(25)	2(17)	4(33)	
Carbomedics	3(8)	1(8)	2(17)	0(0)	
Perimount	25(68)	8(67)	8(67)	9(75)	
Valve Size (mm), n(%)					0.29
19	1(3)	0(0)	0(0)	1(8)	
21	5(14)	3(25)	0(0)	2(15)	
23	15(41)	2(17)	7(58)	6(46)	
25	12(32)	6(50)	3(25)	3(23)	
27	4(11)	1(8)	2(17)	1(8)	
Surgery, n(%)					
Concomitant CABG	14(38)	4(33)	6(50)	4(31)	0.57
Other concomitant procedure**	4(11)	1(8)	1(8)	2(15)	0.55
Use of surgical adhesives	0(0)	0(0)	0(0)	0(0)	1.0

*Serum Leucocytes and Creatinine levels were measured as part of clinical practice ±5days after valve implantation and serum glucose levels were measured on the day of 18F-FDG-PET/CT scan. **Four patients underwent a concomitant procedure with the aortic PHV implantation containing two patients with a MAZE procedure, one patient with a myectomy and additional mitral valve replacement and one patient with pulmonary vene ablation on both sides. ***Statistical difference between the three groups 1, 2 and 3
BMI= Body Mass Index. CABG= Coronary Artery Bypass Grafting. PHV= Prosthetic heart valve. PET=CT Positron emission tomography with computed tomography

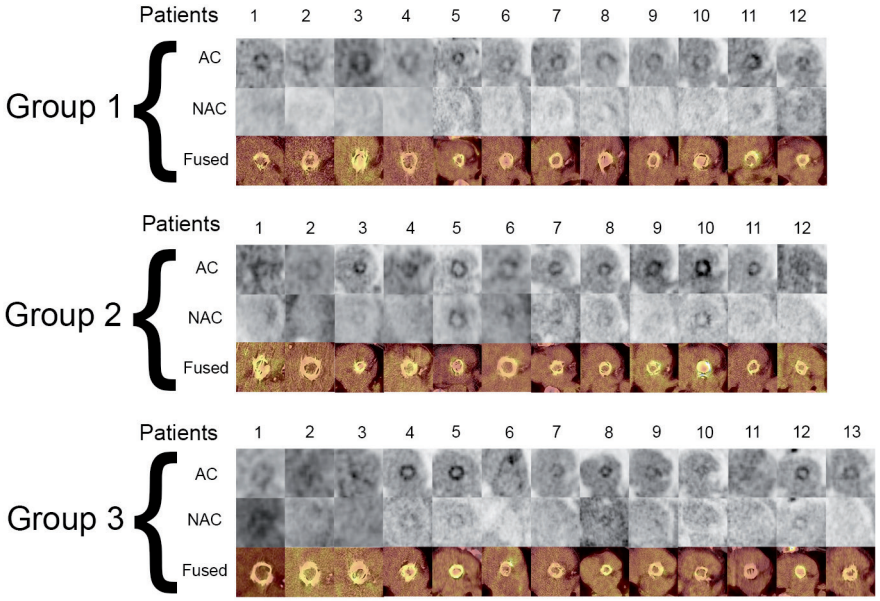

Fig. 1: ^{18}F-FDG uptake around the PHV on reconstructed views in plane with the PHV of attenuation-corrected (AC) images, non-attenuation-corrected (NAC) and fused attenuation-corrected images with CT in all patients. Scaling was set the same for all AC images (0-7MBq).

The ^{18}F-FDG uptake around the PHVs on a reconstructed view in the PHV plane of attenuation-corrected images, non-attenuation-corrected and fused attenuation-corrected images with CT of all patients is shown in figure 1.

Quantitative analyses on the non-EARL attenuation-corrected images showed a SUV_{max} of 4.1±0.8 (mean±SD) and a median[IQR] SUV_{ratio} of 2.0 [1.8-2.2] for all included patients. The SUV_{max} around the PHV was 4.1±0.7, 4.6±0.9 and 3.8±0.7 (mean±SD) in group 1, 2 and 3 respectively, with no significant difference between the 3 groups (p=0.08). The median[IQR] SUV_{ratio} around the PHV was 2.0 [1.9-2.2], 2.0 [1.8-2.6], and 1.9 [1.7-2.0] with no significant difference between the three groups (p=0.81) (table 3). Quantitative analyses on the EARL reconstruction images showed an average SUV_{max} and SUV_{ratio} of 3.6±0.5 and 1.8±0.3 (mean±SD), respectively. SUV_{max} around the PHV was 3.6±0.5, 3.8±0.5 and 3.3±0.6 (mean±SD) in group 1, 2 and 3 respectively, with no significant difference between the 3 groups (p=0.14). Likewise, the SUV_{ratio} around the PHV was 1.8±0.2, 1.8±0.3, and 1.7±0.3(mean±SD) with no significant difference between the three groups either (p=0.41). The minimum and maximum measured SUV_{ratio} in the study population was 1.4 and 2.5 respectively. EARL SUV_{ratio} was <2.3 in 97% and <2.1 in 92% of the cases. The distribution of non-EARL and EARL SUV_{max} and SUV_{ratio} are demonstrated in figure 2.

Table 3: 18F-FDG PET/CT findings for all patients and for each patient per group

	All included patients	Group 1 (5 (±1) weeks after PHV implanta-tion)	Group 2 (12 (±2) week after PHV implanta-tion)	Group 3 (12 (±2) months after PHV implanta-tion)	P-value*
Number of patients	37	12	12	13	
FDG dose, MBq/kg, m[IQR]	166 [145-183]	160 [134-175]	172 [156-181]	180 [140-188]	0.16
Time between FDG dose and start scan (min), m[IQR]	60 [58-64]	59 [57-63]	60 [59-63]	60 [58-66]	0.82
Serum levels of glucose mmol/L (mean±SD)	5.4±0.7	5.5±0.6	5.5±0.8	5.2±0.8	0.47
Preparation according to carbohydrate diet protocol, n(%)	36(97)	11(92)	12(100)	13(100)	0.34
Myocardial suppression, n(%)					0.70
Fully Suppressed	18(49)	7(58)	5(42)	6(46)	
Low uptake	1(3)	1(8)	0(0)	0(0)	
Intermediate uptake	10(27)	2(17)	3(25)	5(38)	
High focal uptake	1(3)	0(0)	1(8)	0(0)	
High diffuse uptake	7(19)	2(17)	3(25)	2(15)	
Elevated uptake elsewhere in the body, n(%)	21(57)	7(58)	9(75)	5(38)	0.34
Visual score PHV (QVSH), n(%)					0.91
None	0(0)	0(0)	0(0)	0(0)	
Low	23(62)	8(67)	7(58)	8(62)	
Intermediate	14(38)	4(33)	5(42)	5(38)	
High	0(0)	0(0)	0(0)	0(0)	
Specific location FDG uptake, n(%)					0.50
Former LCC	1(3)	0(0)	1(8)	0(0)	
Former NCC	1(3)	1(8)	0(0)	0(0)	
Circular	29(78)	8(67)	9(75)	12(92)	
Struts only	5(14)	2(17)	2(17)	1(8)	
Multiple	1(3)	1(8)	0(0)	0(0)	
SUV_{max} PHV (mean±SD)	4.1±0.8	4.1±0.7	4.6±0.9	3.8±0.7	0.08
SUV_{ratio} PHV m[IQR]	2.0[1.8-2.2]	2.0[1.9-2.2]	2.0[1.8-2.6]	1.9[1.7-2.0]	0.81
EARL SUV_{max} PHV (mean±SD)	3.6±0.5	3.6±0.5	3.8±0.5	3.3±0.6	0.14
EARL SUV_{ratio} PHV (mean±SD)	1.8±0.3	1.8±0.2	1.8±0.3	1.7±0.3	0.41

* Statistical difference between the three groups 1, 2 and 3
PHV= Prosthetic heart valve.
MBq/kg= Megabecquerel/kilograms
QVSH= Qualification Visual Score of Hypermetabolism
LCC= Left Coronary Cusp
NCC= Non coronary Cusp
SUVmax= Maximum standardized Uptake Value
SUVratio= Standardized Uptake value ratio (Target to background ratio)
EARL= European Association of nuclear medicine Research Ltd.

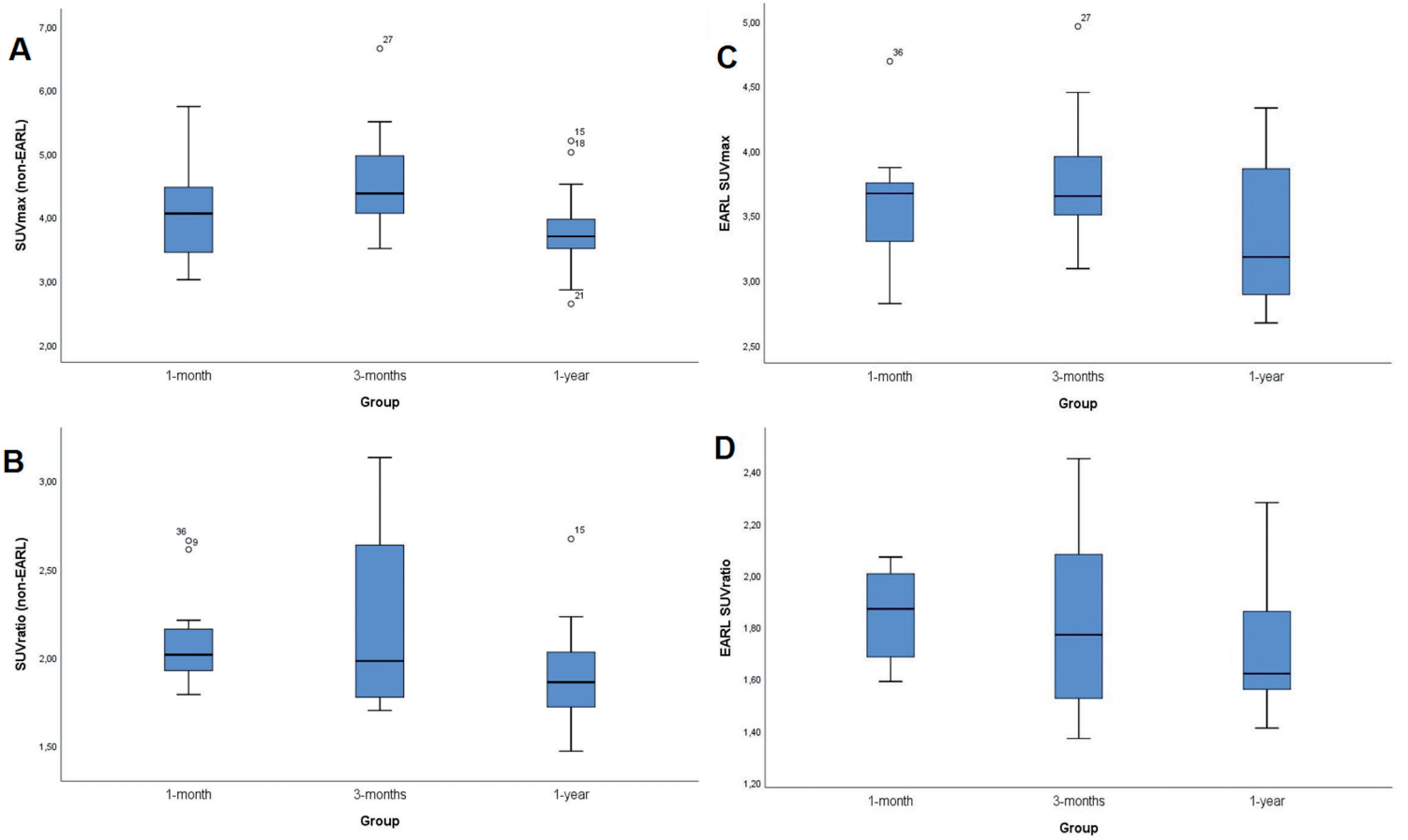

Fig. 2: Boxplots of the non-EARL (A,B) and EARL (C,D) SUV_{max} and SUV_{ratio} measurement distribution in each group. The dots indicated as “15”, “18”, “21” , “27” (A) “9”, “15”, “36” (B) “27” and “36” (C) are outliers in the SUV_{max} and SUV_{ratio} measurements.

Elevated ^{18}F-FDG uptake elsewhere in the body was seen in 21/37 (57%) of patients and was not significantly different between the 3 groups (p=0.18). This elevated ^{18}F-FDG uptake was mainly seen in the thoracic lymph nodes 9/21 (38%) and considered physiological. Other areas of elevated uptake consisted of costal fractures 3/21 (14%), pleural uptake (possible pulmonary nodule) 2/21 (10%), acromioclavicular joint (due to degeneration) 2/21 (10%), thyroid (possible hyperthyroidism) 1/21 (5%), arytenoid (physiological) 1/21 (5%), possible pathological oesophageal uptake 2/21 (10%), diffuse in muscles 1/21 (5%), and focal uptake due to a surgical clip.

Discussion

The present study shows that patients with non-infected aortic PHV have similar low to intermediate mostly circular ^{18}F-FDG uptake around the PHV at 5, 12 and 52 weeks after implantation and a mean±SD SUV_{max} of 4.1±0.8 and a median[IQR] SUV_{ratio} of 2.0[1.8-2.2].

Nowadays, ^{18}F-FDG PET/CT is an important diagnostic method in suspected PHV endocarditis, especially in cases where the diagnosis cannot be confirmed with transthoracic (TTE) or transesophageal echocardiography (TEE). However, in patients with a recent PHV implantation (<3 months), the use of ^{18}F-FDG PET/CT is not advised due to possible false positive findings caused by post-surgical inflammation (2). Misinterpretation of ^{18}F-FDG PET/CT findings could have major inappropriate therapeutic consequences. Patients may be treated while this is not necessary and counter wise not be treated while this is obligatory. Therefore, caution with the interpretation of ^{18}F-FDG PET/CT in the early weeks after PHV implantation is advised, especially in cases of complicated surgery. In such cases, the inflammation response due to the complications could be severe and cause non-diagnostic or false positive ^{18}F-FDG PET/CT results. It is therefore crucial to be able to recognize normal ^{18}F-FDG distribution patterns and establish a quantitative cut-off value for pathological ^{18}F-FDG uptake around the PHV.

Quantitative measurements of ^{18}F-FDG uptake around the PHV in our study demonstrated a median[IQR] SUV_{ratio} of 2.0[1.9-2.2.] for patients at 5 weeks after surgery, with no statistically significant difference compared to 3 months and 1 year (2.0[1.8-2.6] and 1.9[1.7-2.0], respectively; p=0.81). These results corroborate the scarse known literature about this matter. Mathieu et al. (7) reported on a retrospectively included group of 35 patients with aortic PHVs who underwent a PET/CT scan <3 months and >3months after PHV implantation for either oncological imaging, large vessel vasculitis or suspicion of prosthetic valve endocarditis that was subsequently rejected, and found a median SUV_{max} of 3.6 [2.1-8.0, range] and a median SUV_{ratio} of 1.9 [1.3-6.6, range] on non-EARL attenuation-corrected images. No significant difference in SUV_{max} and SUV_{ratio} between the PHVs implanted <3

months and those that were implanted >3 months prior to the PET/CT scan was found (7). However, these results should be interpreted with some caution because: 1) the patient population was diverse and included patients with vasculitis and a rejected suspicion of endocarditis and 2) 24/35 (69%) of the valves were implanted more than 1 year ago. The authors also reported a much higher median SUV_{max} of 4.7 and SUV_{ratio} of 2.7 in the patients with vasculitis compared to the other groups (7). Roque et al (8) have recently presented a prospective analysis of ^{18}F-FDG uptake at 3 different time points in the first year after PHV implantation. The study method had similarities with our study, but there were some differences. Roque et al included also patients post mitral valve implantation, and each patient received 3 times a PET/CT scan in the time periods of 1, 6 and 12 months after valve implantation. Despite these differences, their results also showed no significant difference in ^{18}F-FDG uptake between scans made in the three different time periods and their conclusion that the three months safety period should be reconsidered is in line with our conclusion.

Recently, in a retrospectively collected cohort of 243 patients, we found that the optimal diagnostic cut-off value to diagnose PHV endocarditis for the EARL-standardized SUV_{ratio} was >2.0 (3). In our current study the maximum measured EARL SUV_{ratio} was 2.5 and 97% of scans had an EARL SUV_{ratio} of less than 2.3, indicating that the cut-off value might be slightly higher than the >2.0 reported earlier by Swart et al. in the first year after PHV implantation (3) and also higher than the mean values reported by Mathieu et al. (7).

In our current study, we found only diffuse ^{18}F-FDG uptake around the PHV with mostly a circular pattern (29/37, 78%) and without focal enhancement. The distribution of ^{18}F-FDG can differ widely and its definition is still unclear, however some of the uptake patterns (e.g., diffuse around PHV without focal enhancement) have been associated with physiological uptake after PHV implantation (7). Furthermore, physiological myocardial uptake during ^{18}F-FDG PET/CT can mask adjacent abnormal ^{18}F-FDG uptake around the PHV. Therefore, a prepatory low carbohydrate diet that may be supplemented by an intravenous injection of heparin is necessary for reducing myocardial ^{18}F-FDG uptake in order to avoid false positive ^{18}F-FDG PET/CT results (9-12). In our study, one patient had failed to follow the prepatory low carbohydrate diet and demonstrated indeed a high level of myocardial ^{18}F-FDG uptake making correct measurement of the SUV values more difficult (figure 3).

Our study has some limitations. Eight patients (group 1: n=2, group 2: n=3 and group 3: n=3) received the scan somewhat later than the time frame adjusted for each group. This was due to logistic reasons. Another limitation of this study was that the scan was performed once in every patient and not multiple times in the same patient to actually see a change over time in the uptake patterns and SUV values. This approach was not deemed feasible due to the high radiation dose of multiple PET/CT scans in individual healthy patients this would imply. Furthermore, our study population only included patients with an aortic prosthetic valve,

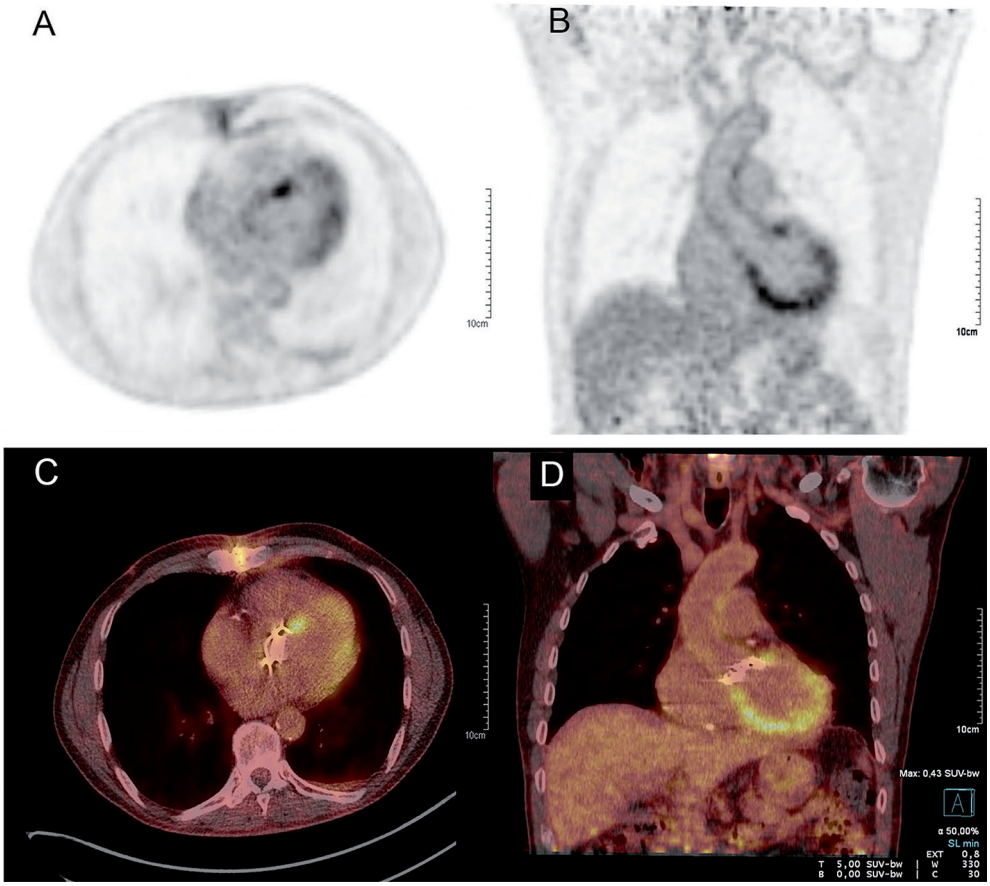

Fig. 3: Attenuation-corrected ^{18}F-FDG PET images (A,B) and fused images (C,D) of a patient with a high level of myocardial ^{18}F-FDG uptake making correct measurements of the SUV values more difficult.

hence we cannot draw any conclusion regarding normal ^{18}F-FDG findings for prosthetic valve in other locations or regarding combined aortic valve and ascending aorta replacements (e.g., Bentall procedure). Excluding obese patients and patients with diabetes mellitus could also be seen as a limitation to the applicability of our results. Both conditions can affect the healing process following surgery and could therefore potentially impact ^{18}F-FDG uptake. However, in order to prevent inadequate glucose levels prior to the PET and restrict the radiation exposure to patients, the exclusion of these patients was necessary. In total 51% of the patients did not have fully suppressed myocardium and this could be seen as a potential confounder to the qualitative and quantitative ^{18}F-FDG measurements.

Although the measurements done by the nuclear medicine physicians were carefully done not to include myocardial uptake, this could not always have been prevented. Thus, this could be seen as a limitation of our study.

In conclusion, non-infected aortic PHV have similar low to intermediate mostly circular perivalvular ^{18}F-FDG uptake at 5, 12 and 52 weeks after implantation and an average SUV_{max} of 4.1±0.8 and a median[IQR] SUV_{ratio} of 2.0[1.8-2.2]. These normal ^{18}F-FDG uptake values and patterns provide further evidence that ^{18}F-FDG PET-CT can be used as a diagnostic tool for the detection of endocarditis even shortly after aortic PHV implantation and the recommendation to not perform PET-CT within the first three months after PHV implantation in the 2015 ESC guidelines for the management of infective endocarditis should be reconsidered.

New knowledge gained

Our study supports previous observations on the normal perivalvular ^{18}F-FDG uptake within the first year after PHV implantation and showed no significant difference in ^{18}F-FDG uptake at 5 weeks, 12 weeks or 52 weeks after implantation. These findings may help clinicians to differentiate between normal and pathological perivalvular ^{18}F-FDG uptake and suggest the use of ^{18}F-FDG PET/CT as an extra imaging tool in the diagnostic workup of patients with recent aortic PHV implantation that are suspected of PHV endocarditis.

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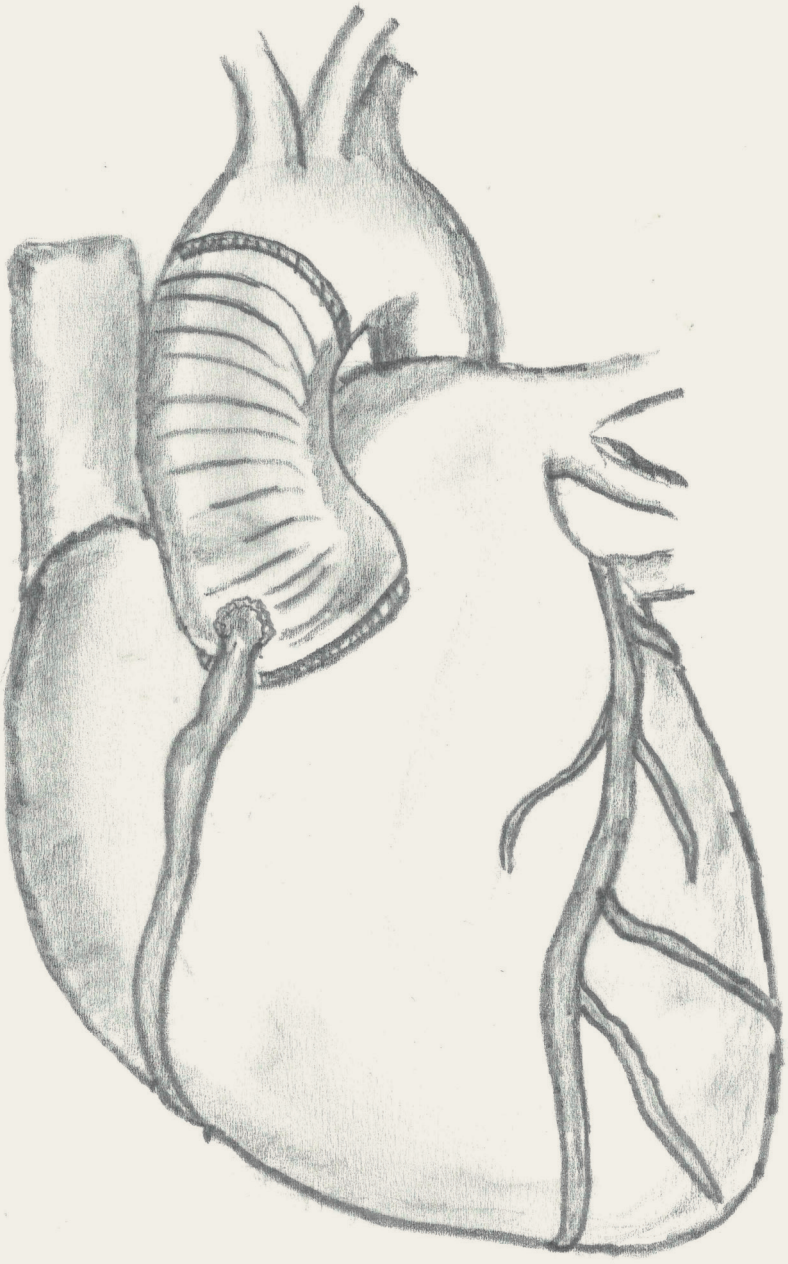

Chapter 7

Normal Imaging Findings after Ascending Aorta Prosthesis Implantation on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography with Computed Tomography

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Abstract

Background: To diagnose abnormal ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) uptake in suspected endocarditis after aortic root and/or ascending aorta prosthesis (ARAP) implantation, it is important to first establish the normal periprosthetic uptake on Positron Emission Tomography with computed tomography (PET/CT).

Methods: Patients with uncomplicated ARAP implantation were prospectively included and underwent ^{18}F-FDG-PET/CT at either 12(±2) weeks(group 1) or 52(±8) weeks(group 2) after procedure. Uptake on three different locations of the prosthesis ("cranial anastomosis (CA)", "prosthetic heart valve(PHV)", "ascending aorta prosthesis (AAP)") was scored visually (none/low/intermediate/high) and quantitatively (maximum Standardized Uptake Value (SUV_{max}) and target to background ratio (SUV_{ratio}).

Results: In total, 20 patients (group 1: n=10, group 2: n=10) (mean age 64±7 years, 70% male) were included. Both groups had similar visual uptake intensity for all measured areas (CA: mostly low-intermediate (16/20(80%),p=0.17; PHV: low-intermediate (16/20(80%),p=0.88; AAP: low-intermediate (19/20(95%)), p=0.48). SUV_{max} for CA was 5.6[4.1-6.1] and 3.8[3.1-5.9](median[IQR],p=0.19) , and around PHV 5.0[4.1-5.7] and 6.3[4.6-7.1](p=0.11) for groups 1 and 2 respectively. SUV_{ratio} for CA was 2.8[2.3-3.2] and 2.0[1.7-2.6](median[IQR],p=0.07) and around PHV 2.5[2.4-2.8] and 2.9[2.3-3.5](median[IQR],p=0.26) for groups 1 and 2 respectively.

Conclusion: No significant differences were observed between PET/CT findings at 3 months and 1 year after ARAP implantation, warranting caution in interpretation of PET/CT in the first year after implantation.

Introduction

Infective endocarditis (IE) and especially prosthetic valve endocarditis (PVE) is difficult to diagnose(1, 2). The diagnosis becomes even more challenging when an implanted aortic prosthetic heart valve is combined with an ascending aorta and root conduit (Bentall graft) or a supra coronary ascending aorta prosthetic replacement (SCAR), since there are no specific criteria for the diagnosis of infection of these prostheses(3). Normal imaging findings on computed tomography angiography (CTA) after a recent Bentall procedure, often show periaortic fluid to be present around the prosthesis (4, 5). ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography with computed tomography (PET/CT) is nowadays used as an additional diagnostic tool for the diagnosis of PVE according to the latest European Society of Cardiology (ESC) guidelines for IE(1). However, these guidelines do not mention the use of ^{18}F-FDG PET/CT for the detection of aortic root and/or ascending aorta prosthesis (ARAP) infection, while this technique is increasingly used. Recently, two prospective studies described the normal ^{18}F-FDG uptake patterns and intensities around prosthetic heart valves (PHVs) and showed no significant differences between ^{18}F-FDG uptake around prosthetic valves at different time points within the first year after implantation(6, 7). It is generally assumed that normal healing response after replacement of the ascending aorta and root will result in ^{18}F-FDG uptake at the operated area similar to what is seen in prosthetic valve implantation. It is not well-known how long this process will take and how long the PET-CT may be relatively unreliable. However, the normal ^{18}F-FDG uptake intensity and pattern on ARAP needs to be known, to enhance correct interpretation of ^{18}F-FDG PET/CT scans in patients with suspected infection. In order to determine the normal ^{18}F-FDG uptake patterns and intensity around ARAP, we prospectively assessed the visual and quantitative ^{18}F-FDG uptake at two different time points and three different locations in the aorta in the first year after Bentall and SCAR procedures.

Materials and methods

Patient selection and classification

In this prospective cross-sectional study, patients 50 years or older who had undergone an uncomplicated Bentall or SCAR procedure were included. An uncomplicated procedure was defined as a procedure with no complications during or directly after surgery. A detailed list of the inclusion and exclusion criteria is presented in table 1. The medical ethics committee approved the study (NL42743.041.12). All patients provided written informed consent. Patients were included and underwent PET-CT after the Bentall/SCAR procedure at either 12(±2) weeks (group 1) or 52(±8) weeks (group 2).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 50 years • Patients after uncomplicated Bentall/SCAR procedure in aortic position including a PHV • Normal routine follow up TTE (standardly performed 5 days after surgery) or intra-operative TEE. With no signs of obstruction, endocarditis or significant paravalvular leakages. • Weight < 110 kg	• Diabetes Mellitus • Mild contractile dysfunction of the left and/ or right ventricle (Eyeballing, Ejection fraction <45 %, TAPSE <14 mm) • Active cardiac decompensation • Uncontrolled cardiac arrhythmias • Suspicion of active endocarditis • Previous participation in scientific studies using radiation. • (Possible) pregnancy in pre-menopausal women above 50 years not on reliable birth control therapy. • Use of pericardial patches and re-operation of aortic PHV in past medical history • Refusal to be informed about potential FDG-PET findings

SCAR= Supra coronary ascending aorta replacement
PHV= Prosthetic heart valve
TTE= Transthoracic echocardiogram
TEE= Transesophageal echocardiogram
TAPSE= Tricuspid annular plane systolic excursion
FDG-PET= Fluorodeoxyglucose-Positron emission tomography

Included patients did not have any clinical signs of IE or other infection (fever, shivers, dyspnea, etc) at the time of the ^{18}F-FDG PET/CT.

Image acquisition

^{18}F-FDG PET/CT

To induce free fatty acid metabolism and suppress myocardial glucose metabolism, patients followed a 12-hours low carbohydrate diet followed by 12 hours fasting (8-10). Thereafter, patients received an intravenous ^{18}F-FDG-injection of 2.0 MBq/kg. Patients were hydrated with 1000 ml of water 1 hour prior to image acquisition. Blood glucose levels were checked before ^{18}F-FDG injection and the limit was set to 8.9 mmol/l. Approximately 1 hour after ^{18}F-FDG injection, the PET/CT was performed using a Biography Sensation 16scanner (SIEMENS Medical, Germany). Before the PET acquisition, a low dose CT-scan was performed for attenuation correction. A PET-scan of the heart was then obtained with 3-minute acquisitions per bed position using a 3-dimensional acquisition mode. Attenuation corrected PET images were reconstructed with an ordered-subset expectation-maximization iterative reconstruction algorithm.

Image analysis and interpretation

^{18}F-FDG PET/CT analysis

Uptake of ^{18}F-FDG on three different levels (cranial anastomosis, around the PHV and on the ascending aorta prosthesis) were scored visually, and if feasible also quantitatively

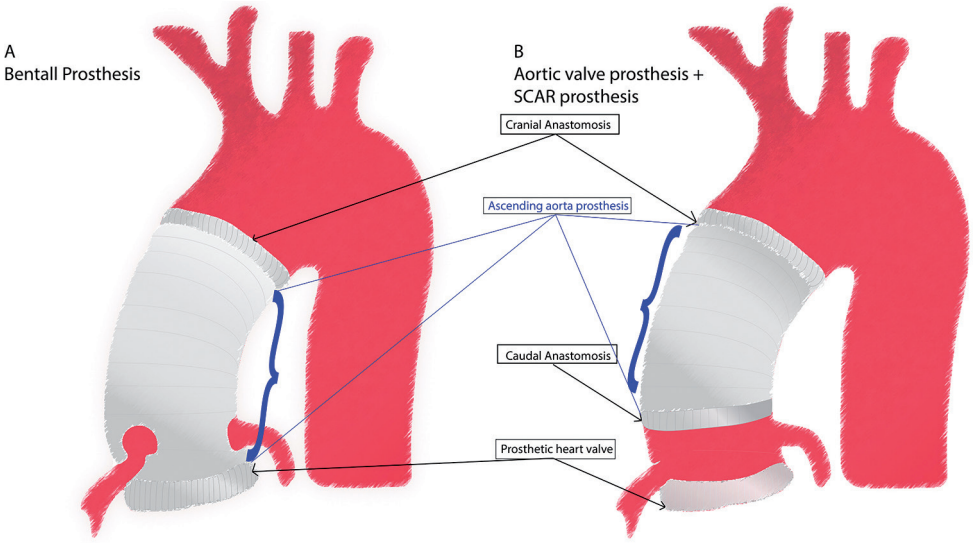

Fig. 1: Schematic view of the Bentall prosthesis (A) and SCAR prosthesis + aortic prosthetic heart valve (B) and the areas of measured FDG activity indicated by arrows

for all patients by experienced nuclear medicine physicians (TM, LG) who were blinded for group allocation (Figure 1). Additional visual and quantitative measurements were also made at the caudal anastomosis for patients with a SCAR procedure including a PHV implantation. For patients with a Bentall procedure, the caudal anastomosis equalled the area of the PHV. The measured area of "the ascending aorta prosthesis" was defined as the part of the prosthesis between the cranial and caudal anastomosis. Figure 1 illustrates the measured levels on both prostheses. For qualitative analyses, the Qualification Visual Score for Hypermetabolism (QVSH) was used, scoring the uptake as "none" (no or less than blood pool uptake), "low" (more than blood pool uptake but less than in the liver), "intermediate" (more than liver uptake), or "high" (intense uptake). "Blood pool" uptake was defined as the mean uptake in the blood pool of the descending aorta at the level of the left atrium. Distribution patterns were scored as either "focal" (solitary ^{18}F-FDG uptake spot) or "multi focal" (>1 solitary ^{18}F-FDG uptake spot) versus "diffuse" (>1 location of ^{18}F-FDG uptake that cannot be differentiated as solitary spots) which could be homogeneous (overall same level of ^{18}F-FDG uptake intensity) or heterogeneous (different levels of ^{18}F-FDG uptake intensity). Quantitative analyses were performed by measuring the maximum Standardized Uptake Value (SUV_{max}) and target to background ratio (SUV_{ratio}) on standardized European Association of Nuclear Medicine Research Ltd. (EARL) and non-EARL reconstructions using commercially available software (Carestream v12.2.2.1025). SUV_{max} was measured in an automated volume of interest (VOI) around both anastomoses, which was visually verified to include the whole anastomotic area. The SUV_{ratio} was then calculated as the ratio of the SUV_{max} and the mean SUV in the blood pool of the descending aorta, taking care not to include the vessel wall.

Myocardial suppression was scored as “fully suppressed” (no uptake), “low” (more than mediastinal uptake but less than in the liver), “intermediate” (more than liver uptake), “high focal” (much more than liver uptake, but focal), “high diffuse” (much more than liver uptake, diffuse).

Statistics

Descriptive statistics were used for analysis of the outcomes. For continuous variables, means and standard deviations (SD) were used in case of normal distribution. In case of non-normal distribution, medians and interquartile ranges (IQR) were used. The IQR and confidence interval (CI) were denoted in square brackets. Comparisons between groups were made using the Chi-square test for categorical variables and non-parametric test (Mann Whitney U) for continuous variables. A significance level of p=0.05 and 95% confidence intervals (CI) were used.

Results

Patients’ characteristics and classification

A total of 20 patients were included in either group 1 (n=10) or group 2 (n=10). Age was (median with IQR) 64[60-71] years, (group 1= 64[60-70]; group 2= 62[59-73]) and most of the patients were male (n=14, 70%). A Bentall procedure was performed in 14/20(70%) patients (group 1=6, group 2=8), and SCAR in 6/20(30%) patients (group 1=4, group 2=2). All patients with SCAR also underwent a concomitant aortic valve replacement (AVR). There were 9 (45%) biological and 11 (55%) mechanical prosthetic valves, not significantly different between groups (p=0.18). Surgical adhesives such as BioGlue that are known to be FDG-avid, were not used during any of the implantations. No patient was suspected of having endocarditis at the time of operation or the PET/CT scan. Baseline characteristics of the participants are summarized in table 2.

^{18}F-FDG PET/CT findings

The median time between the surgery and ^{18}F-FDG PET/CT was 91 [88-95] and 373 [358-414] days for group 1 and 2 respectively (p<0.01). Mean±SD ^{18}F-FDG dosage was 164±30 MBq and not significantly different between the groups (p=0.08). Preparation according to carbohydrate diet protocol was followed by all patients. In table 3, a detailed presentation of the myocardial suppression as well as visual analysis of the ARAP in all patients is provided.

Figure 2 presents an overview of FDG activity around the prosthesis in all 20 patients included in this study. The QVSH around the three measured levels (cranial anastomosis, at the PHV and at the ascending aorta prosthesis) showed no significant difference between the 2 groups (p=0.17; p=0.88 and p=0.48 respectively) and was scored primarily as low or

Table 2: Baseline characteristics of all patients and of patients in groups 1 and 2

	All included patients	Group 1 (12 (±2) weeks after prosthesis implantation)	Group 2 (12 (±2) months after prosthesis implantation)	P-value***
Number of patients	20	10	10	
Age, median [IQR], years	64[60-71]	64[60-70]	62[59-73]	0.38
Gender, n(%)				1.0
Male	14(70)	7(70)	7(70)	
Female	6(30)	3(30)	3(30)	
BMI, median [IQR], kg/m^2	26[23-29]	24[23-28]	28[24-31]	0.12
Days between surgery and PET/CT, median [IQR], days	218[90-374]	91[88-95]	373[358-414]	<0.01
Laboratory results*				
Serum levels of leucocytes x109 /L, median [IQR]	10.8[8.9-12.9]	10.6[9.8-13.6]	10.8[8.5-12.8]	0.58
Serum levels of creatinine µmol/L, median [IQR]	82[62-91]	77[58-105]	86[67-90]	0.80
Medical History, n(%)				
Hypertension	2(10)	1(10)	1(10)	1.0
Atrial fibrillation	4(20)	2(20)	2(20)	1.0
Hearth failure	0(0)	0(0)	0(0)	NA
Myocardial infarction	1(5)	1(10)	0(0)	0.31
Prior thoracic surgery	0(0)	0(0)	0(0)	NA
Procedure				0.33
Bentall	14(70)	6(60)	8(80)	
AVR+SCAR	6(30)	4(40)	2(20)	
PHV type, n(%)				
Mechanical	11(55)	4(40)	7(70)	0.18
Biological	9(45)	6(60)	3(30)	
Valve manufacturer, n(%)				
St. Jude	11(55)	4(40)	7(70)	0.18
Perimount	9(45)	6(60)	3(30)	
Valve Size median [IQR](mm)	26[23-27]	26[23-27]	26[23-28]	0.91
Aorta prosthetic size median [IQR](mm)	28[26-30]	29[27-30]	28[26-29]	0.22
Surgery, n(%)				
Concomitant CABG	17(85)	8(80)	9(90)	0.53
Other concomitant procedure**	9(45)	6(60)	3(30)	0.37
Use of surgical adhesives	0(0)	0(0)	0(0)	NA

PHV= Prosthetic heart valve
AVR= Aortic valve replacement
BMI= Body Mass Index
PET/CT = Positron emission tomography with computed tomography
SCAR= Supra coronary aortic replacement
CABG= Coronary artery bypass graft
IQR= Interquartile range
SD= Standard deviation
*Serum Leucocytes and Creatinine levels were measured as part of clinical practice ±5days after surgery
**Nine patients underwent a concomitant procedure with the aortic PHV implantation containing two patients with a left atrial appendage amputation and pulmonary vene isolation procedure, seven patients with a hemiarch replacement.
***Statistical difference between the three groups 1 and 2

Table 3: Visual ^{18}F-FDG PET/CT findings for all patients and for each patient per group

	All included patients	Group 1 (12 (±2) weeks after prosthesis implantation)	Group 2 (12 (±2) months after prosthesis implantation)	P-value*
Number of patients	20	10	10	
FDG dose, MBq/kg, (mean±SD)	164 ±30	152 ± 20	176±34	0.08
Time between FDG dose and start scan (min), m[IQR]	58 [57-62]	58 [57-63]	59 [57-62]	0.77
Serum levels of glucose mmol/L (mean±SD)	5.6±0.6	5.8±0.5	5.5±0.7	0.23
Preparation according to carbohydrate diet protocol, n(%)	20(100)	10(100)	10(100)	1.0
Myocardial suppression, n(%)				0.33
Fully Suppressed	11(55)	5(50)	6(60)	
low uptake	2(10)	2(10)	0(0)	
Intermediate uptake	3(15)	1(10)	2(20)	
High focal uptake	0(0)	0(0)	0(0)	
High diffuse uptake	4(20)	2(20)	2(20)	
Visual score cranial anastomosis (QVSH), n(%)				0.17
None	2(10)	0(0)	2(20)	
Low	10(50)	4(40)	6(60)	
Intermediate	6(30)	4(40)	2(20)	
High	2(10)	2(20)	0(0)	
Specific FDG uptake pattern, n(%)				0.94
Focal	7(35)	4(40)	3(30)	
Multifocal	0(0)	0(0)	0(0)	
Diffuse homogeneous	5(25)	3(30)	2(20)	
Diffuse heterogeneous	6(30)	3(30)	3(30)	
Visual score PHV (QVSH), n(%)				0.88
None	0(0)	0(0)	0(0)	
Low	9(45)	5(50)	4(40)	
Intermediate	7(35)	3(30)	4(40)	
High	4(20)	2(20)	2(20)	
Specific FDG uptake pattern, n(%)				0.31
Focal	1(5)	1(10)	0(0)	
Multifocal	0(0)	0(0)	0(0)	
Diffuse homogeneous	19(95)	9(90)	10(100)	
Diffuse heterogeneous	0(0)	0(0)	0(0)	
Visual score total prosthesis (QVSH), n(%)				0.48
None	1(5)	1(10)	0(0)	
Low	12(60)	5(50)	7(70)	
Intermediate	7(35)	4(40)	3(30)	
High	0(0)	0(0)	0(0)	
Specific pattern FDG uptake, n(%)				1.0
Focal	0(0)	0(0)	0(0)	
Multifocal	0(0)	0(0)	0(0)	
Diffuse homogeneous	18(90)	9(90)	9(90)	
Diffuse heterog.	2(10)	1(10)	1(10)	

* Statistical difference between groups 1 and 2
QVSH= Qualification Visual Score of Hypermetabolism

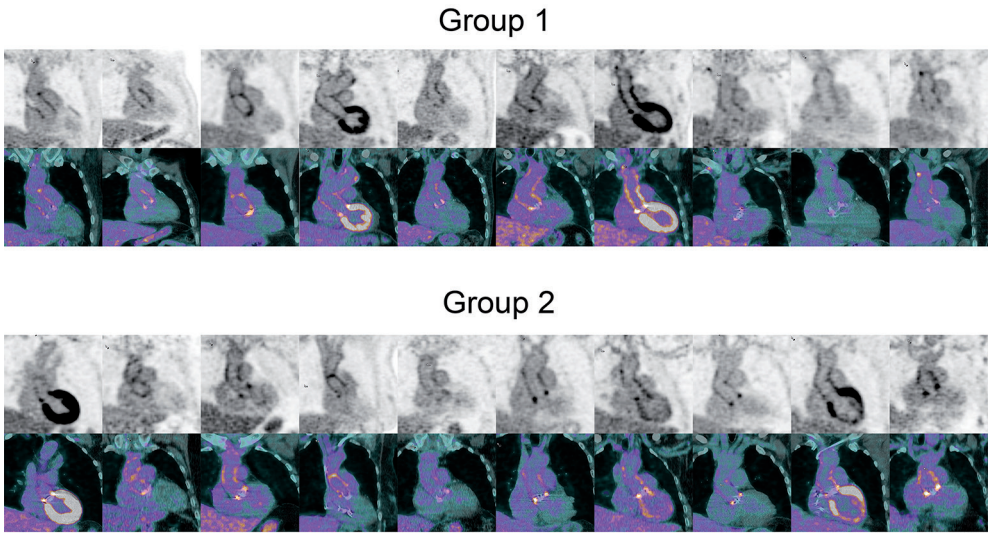

Fig. 2: ^{18}F-FDG uptake around the prosthesis on coronal views of attenuation-corrected (AC) images and fused attenuation-corrected images with CT in all patients. Scaling was set the same for all AC images and represents SUV with a range of 0-7.

intermediate (16/20 (80%), 16/20 (80%) and 19/20 (95%) respectively). Details of the QVSH and the distribution patterns are provided in table 3. Examples of the uptake patterns are demonstrated in figure 3 with an example of diffuse homogeneous pattern in group 1 versus group 2 in figure 4.

In table 4, a detailed presentation of the quantitative analysis of ^{18}F-FDG uptake is provided.

With the exception of SUV_{ratio} of the cranial anastomosis on the EARL reconstructed images, no significant difference was found in the quantitative analysis of the three measured levels between the 2 groups.

Additional quantitative analysis of the caudal anastomosis for patients after a SCAR procedure (n=6) showed a median SUV_{max} of 4.7[3.8-5.5] and SUV_{ratio} of 2.2[2.1-2.6] on the attenuation-corrected images. For patients in group 1 the median SUV_{max} was 4.2[3.5-6.4] and the median SUV_{ratio} 2.3[2.2-3.3]. For the 2 patients in group 2 the median SUV_{max} and SUV_{ratio} was 4.9 and 2.1, respectively. No significant difference in SUV_{max} or SUV_{ratio} was seen between the 2 groups (SUV_{max}: p=0.53, SUV_{ratio}: p=0.27). On the EARL reconstructed images the median SUV_{max} was 3.6[3.1-3.9] and the median SUV_{ratio} 1.8[1.7-1.8] with no significant difference between the groups (SUV_{max}: p=0.27, SUV_{ratio}: p=0.80).

Quantitative analysis of the ^{18}F-FDG uptake on the ascending aorta prosthesis could not be performed due to the diffuse uptake pattern in all cases.

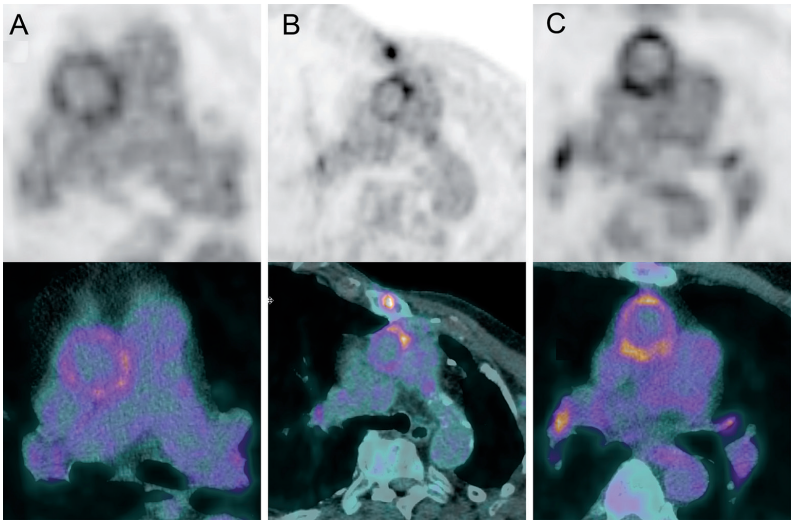

Fig. 3: Examples of ^{18}F-FDG uptake patterns (A: diffuse homogeneous, B: focal, C:diffuse heterogeneous) around the cranial anastomosis. Scaling was set the same for all images and represents SUV with a range of 0-7.

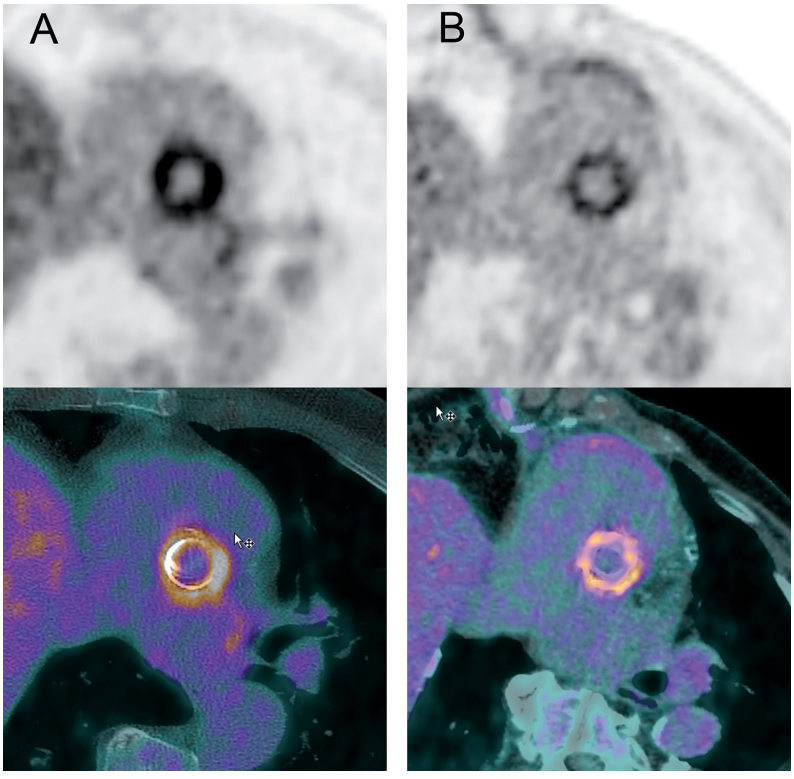

Fig. 4: Examples of the diffuse homogeneous ^{18}F-FDG uptake pattern around the prosthetic heart valve on a patient from group 1 (A) and a patient from group 2 (B). Scaling was set the same for all images and represents SUV with a range of 0-7.

Table 4: Quantitative ^{18}F-FDG PET/CT findings for all patients and for each patient per group

	All included patients	Group 1 (12 (±2) weeks after prosthesis implantation)	Group 2 (12 (±2) months after prosthesis implantation)	P-value*
Number of patients	20	10	10	
SUVmax Cranial anastomosis (mean±SD)	4.7[3.3-6.1]	5.6[4.1-6.1]	3.8[3.1-5.9]	0.19
SUVratio Cranial anastomosis (mean±SD)	2.3[1.9-3.0]	2.8[2.3-3.2]	2.0[1.7-2.6]	0.07
EARL SUVmax Cranial anastomosis (mean±SD)	3.4[2.8-4.1]	3.8[3.4-4.2]	3.1[2.5-3.6]	0.08
EARL SUVratio Cranial anastomosis (mean±SD)	1.7[1.4-1.9]	1.8[1.7-2.0]	1.5[1.3-1.8]	0.04
SUVmax PHV median [IQR]	5.5[4.2-6.8]	5.0[4.1-5.7]	6.3[4.6-7.1]	0.11
SUVratio PHV median [IQR]	2.6[2.4-3.3]	2.5[2.4-2.8]	2.9[2.3-3.5]	0.26
EARL SUVmax PHV median [IQR]	4.2[3.4-5.0]	4.1[3.2-4.6]	4.5[3.7-5.6]	0.21
EARL SUVratio PHV median [IQR]	2.1[1.7-2.5]	1.9[1.7-2.2]	2.3[1.8-2.6]	0.21

* Statistical difference between groups 1 and 2
PHV= Prosthetic heart valve
MBq/kg= Megabecquerel/kilograms
SUVmax= Maximum standardized Uptake Value
SUVratio= Standardized Uptake value ratio (Target to background ratio)
EARL= European Association of nuclear medicine Research Ltd.

Discussion

The present study shows that in patients with ARAP, ^{18}F-FDG uptake is present in the first year after surgery and has a homogeneous diffuse pattern and low to intermediate intensity on different areas of the prosthesis with no clear difference for any of the measured levels on both visual and quantitative analyses between the two groups (3 months vs 1 year after implantation) with exception of a small difference in the EARL SUV_{ratio} at the cranial anastomosis .

Since the inclusion of ^{18}F-FDG PET/CT in the ESC guidelines of 2015, this imaging tool has become an important diagnostic method in suspected endocarditis in patients with a PHV. However, in patients with a concomitant ARAP which may be part of the infection process of IE or be solely infected, the value of ^{18}F-FDG PET/CT is yet to be assessed. Misinterpretation of ^{18}F-FDG PET/CT in patients with suspected infected ARAP can have severe therapeutic and prognostic consequences. Physiological ^{18}F-FDG uptake due to normal healing response after surgery could be confused with pathological uptake or vice versa; pathological ^{18}F-FDG uptake due to infection could falsely be interpreted as physiological uptake after recent surgery. Therefore, normal ^{18}F-FDG uptake around the ascending prosthesis that is due to normal healing response after surgery, and its level of presence over the course of time after surgery, needs to be clarified in order to differentiate between physiological

and pathological uptake intensity and pattern. One of the potential ways to differentiate between physiological and pathological ^{18}F-FDG uptake, is to treat patients with antibiotics if there is suspicion of pathological uptake and to repeat the PET/CT after 6 weeks. If the ^{18}F-FDG uptake has not changed under antibiotic treatment, the uptake is probably false positive and in case of reduction of uptake intensity and form, the uptake is most certainly true positive. However, this way of differentiation is based on common sense and needs to be determined by studies and/or clinical trials and although logical, this approach is not preferred in clinical practice because of the side effects and costs that come along with antibiotic treatment. Follow-up studies should be based in an adequate interpretation, standardization and reproducibility of the images and not in therapeutic response.

The usefulness of ^{18}F-FDG PET/CT in suspected ARAP is described in the literature, however this is limited to small case series and case reports(11-13). Lucinian et al. demonstrated in a retrospective series of 68 PET/CT's made for suspected aortic root infection, that heterogeneous uptake pattern with a high target to background ratio is associated with infection compared to non-infected aortic roots that had a more homogeneous uptake pattern with a relatively lower target to background ratio(13). However, caution in interpretation of this data is needed for determination of normal ^{18}F-FDG uptake since all the included patients had suspicion of infection. In our study we included only patients with no suspicion of infection and so demonstrating only physiological ^{18}F-FDG patterns and intensity.

Roque et al. and our previous work recently demonstrated the normal ^{18}F-FDG uptake patterns and intensity around prosthetic heart valves in the first year after prosthetic valve implantation in patients that did not undergo associated aortic surgery (6, 7). Both studies found that ^{18}F-FDG uptake shortly after valve implantation is relatively low and does not differ from the uptake 1 year after the implantation. Compared to the results of our current study, this is similar to the ^{18}F-FDG uptake for the cranial anastomosis of the ascending aorta prosthesis, and around the PHV. Very recently, a new study presented the first attempt to provide normal ^{18}F-FDG uptake patterns on ascending aortic prosthetic grafts in the first year after implantation(14). This study corresponds in some ways with our study, however there are some differences. First, some patients had undergone different types of surgery compared to our study (e.g., David procedure, supracoronary graft without PHV implantation and reoperation), second, the post-operative PET/CT scans were made on different time points after surgery , and finally, the ^{18}F-FDG uptake was measured for the total prosthesis only and not separately for the graft anastomoses. Their results showed a slight decrease in ^{18}F-FDG uptake in the first year after surgery with no distinctive ^{18}F-FDG uptake pattern which can be linked to non-infected prostheses.

Quantitative analyses on different locations of the ARAP showed only one small difference (EARL SUV_{ratio} of the cranial anastomosis) that was statistically significant and lower in the group 2 compared to group 1. Although, other quantitative analyses of the cranial anastomosis showed no significant difference between the groups, the p-values were close to 0.05 and may become significantly different if the sample size was larger. This could mean that the ^{18}F-FDG uptake on the cranial anastomosis could decrease over time. However, this conclusion cannot be made based on the results of this study. Whether the ^{18}F-FDG uptake would decrease over a longer period of time than the first year is yet to be clarified with further research. However, theoretically if there was no use of surgical adhesives the inflammation process after surgery should decrease over time which can lead to decrease in ^{18}F-FDG uptake.

Our study has some limitations, with the most obvious being the small sample size of the study. However, since little is known about normal ^{18}F-FDG uptake around ARAP and the importance of normal reference values for correct interpretation of ^{18}F-FDG PET-CT in suspected endocarditis we feel the results provide valuable and clinically relevant information. A limitation of this study was that the scan was performed once in every patient and not multiple times in the same patient to actually see a change over time in the uptake patterns and SUV values. This approach was not deemed feasible due to the high radiation dose of multiple PET/CT scans in individual healthy patients. Excluding obese patients and patients with diabetes mellitus could also be seen as a limitation to the applicability of our results. Both conditions can affect the healing process following surgery and could therefore potentially impact ^{18}F-FDG uptake. However, in order to prevent inadequate glucose levels prior to the PET and restrict the radiation exposure to patients, the exclusion of these patients was necessary. Furthermore, surgical adhesives such as Bioglue were not used in any patient, and this may impact the applicability of the results. Although all of the included patients underwent a prepatory low carbohydrate diet for reducing myocardial uptake, 4 of the patients still had “high diffuse” ^{18}F-FDG uptake of the myocardium and in total 45% of the patients did not have fully suppressed myocardium and this could be seen as a potential confounder to the qualitative and quantitative ^{18}F-FDG measurements, especially around the PHV.

In conclusion, after ARAP ^{18}F-FDG uptake seems to remain present in the first year after surgery with a low to intermediate intensity and mostly homogeneous diffuse patterns. There is no clear difference between patients scanned 3 months and 1 year after surgery. The use of ^{18}F-FDG PET-CT in the first year after ascending aorta prosthesis implantation for the detection of infection of such prosthesis needs to be done carefully taking the normal variability into account to avoid mistakes. More studies are required in order to clarify the utility of PET/CT in the diagnosis of ARAP infection.

New knowledge gained

Our study provides, as one of the first prospective studies, the normal ^{18}F-FDG uptake of the ascending aortic prosthesis in the first year after implantation. These findings may help clinicians in the interpretation of ^{18}F-FDG PET-CT in patients with suspected infection of the ascending aorta prosthesis.

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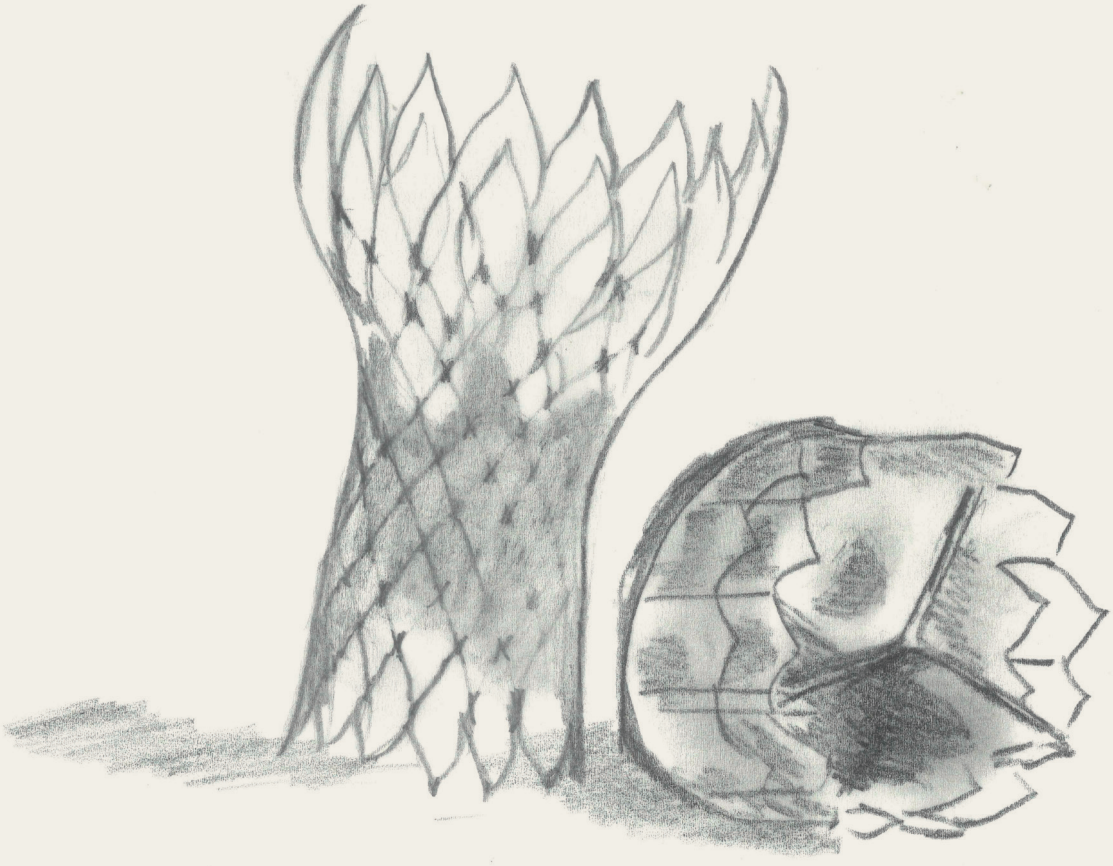

Chapter 8

Added value of ^{18}F-FDG-PET/CT and cardiac CTA in suspected transcatheter aortic valve endocarditis

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Abstract

Backgrounds: Transcatheter-implanted aortic valve infective endocarditis (TAVI-IE) is difficult to diagnose when relying on the Duke Criteria. Our aim was to assess the additional diagnostic value of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron-emission/computed tomography (PET/CT) and cardiac computed tomography angiography (CTA) in suspected TAVI-IE.

Methods: A multicenter retrospective analysis was performed in all patients who underwent ^{18}F-FDG-PET/CT and/or CTA with suspected TAVI-IE. Patients were first classified with Duke Criteria and after adding ^{18}F-FDG-PET/CT and CTA with European Society of Cardiology (ESC) criteria. The final diagnosis was determined by our Endocarditis Team based on ESC guideline recommendations.

Results: Thirty patients with suspected TAVI-IE were included. ^{18}F-FDG-PET/CT was performed in all patients and Cardiac CTA in 14/30. Using the Modified Duke Criteria, patients were classified as 3% rejected (1/30), 73% possible (22/30) and 23% definite (7/30) TAVI-IE. Adding ^{18}F-FDG-PET/CT and CTA supported the reclassification of 10 of the 22 possible cases as “definite TAVI-IE” (5/22) or as “rejected TAVI-IE” (5/22). This changed the final diagnosis to 20% rejected (6/30), 40% possible (12/30) and 40% definite (12/30) TAVI-IE.

Conclusions: Addition of ^{18}F-FDG-PET/CT and/or CTA changed the final diagnosis in 33% of patients and proved to be a valuable diagnostic tool in patients with suspected TAVI-IE.

Introduction

Transcatheter aortic valve implantation (TAVI) is now an accepted and widely applied treatment for aortic valve stenosis in selected patient populations(1). As a major complication, prosthetic heart valve endocarditis (PVE) after a TAVI (TAVI-IE) has been reported to occur with an incidence of 1.6 events per 100 person-years(2). However, the timely diagnosis of this serious disease remains a challenge when using only the modified Duke Criteria, because transthoracic or transesophageal echocardiography (TTE and TEE) may be impaired by artifacts (acoustic shadowing/reverberation) caused by the metallic stent around the valve.

The most recent European Society of Cardiology (ESC) guidelines for infectious endocarditis introduced ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron-emission/computed tomography (PET/CT) and cardiac computed tomography angiography (CTA) as additional diagnostic tools for suspected PVE(3). For surgically implanted prosthetic valves, several reports have described the additional value of ^{18}F-FDG-PET/CT (both visual and quantitative assessment) and CTA in diagnosing PVE as well as how to acquire and interpret the images(4-8). In suspected TAVI-IE these additional imaging tools also may have diagnostic value resulting in a different treatment strategy, however reports on TAVI-IE are still very scarce(9).

The purpose of this study was to assess the additional diagnostic value of ^{18}F-FDG-PET/CT and/or cardiac CTA in patients suspected of TAVI-IE when added to the modified Duke Criteria.

Materials and Methods

Patient selection

All patients with a history of TAVI who were referred to six different hospitals and underwent either ^{18}F-FDG-PET/CT and/or cardiac CTA for suspicion of TAVI-IE were retrospectively included in this study. The institutional medical ethics committee approved the study and waived the need for informed consent.

Patient classification

All data were extracted from the electronic patient records in each hospital. Both the modified Duke Criteria (echocardiographic findings, blood cultures and clinical features) and the 2015 ESC-criteria (modified Duke Criteria *with* the addition of ^{18}F-FDG-PET/CT and CTA) were used to score each patient and give them interim diagnoses (3). The final diagnosis (either rejected, possible or definite TAVI-IE) was established by consensus via the multidisciplinary Endocarditis Team in each hospital, using the latest ESC-criteria and all

clinical records. This meeting was scheduled within 1-7 days after all clinical data (including PET/CT and the eventual CTA) were available. Participants of this multidisciplinary meeting included at least a cardiologist, cardiothoracic surgeon, an infectious disease specialist and a cardiac radiologist/nuclear medicine physician.

Blood cultures

Blood culture results from the period in which patients were hospitalized were included and used for analysis. Blood cultures were deemed positive according to the modified criteria in the latest ESC guidelines for infective Endocarditis(3).

Echocardiography

Either TTE, TEE or both were performed in all included patients, following the current guidelines. The examinations were reported by a certified cardiologist as part of clinical practice and the clinical reports were used for this study. TTE/TEE was considered positive if at least one echo demonstrated the presence of an anatomical and/or echocardiographic criteria for endocarditis according to the ESC-guidelines (3).

Image acquisition

^{18}F-FDG-PET/CT

Patients followed a 24-hour low-carbohydrate diet (of which the last 12 hours were spent fasting) to induce free fatty acid metabolism and suppress glucose metabolism in the myocardium (10-12). One hour after an intravenous ^{18}F-FDG injection (on average 215 megabecquerel (MBq)), a total body or skull-midthigh ^{18}F-FDG-PET/CT scan was acquired using a Siemens Biograph mCT/mCT flow or Philips Gemini TF camera system. Additionally, a low dose CT was performed for attenuation correction.

CT Angiography

CTA imaging was performed on a dual-source CT scanner (Siemens, SOMATOM FORCE or Flash). Scans were performed either with retrospective ECG-gating or a dedicated CT acquisition protocol with ECG gating tailored to the imaging of prosthetic heart valves to provide optimal image quality at minimal radiation exposure(13).

Image analysis and interpretation

PET analysis

Visual analyses of ^{18}F-FDG-PET/CT images had been performed by a nuclear medicine physician as part of clinical practice, while additional quantitative ^{18}F-FDG-PET/CT analyses were performed by an experienced nuclear medicine physician (AS, RS).

The maximum standardized uptake value (SUVmax) was measured in an automated volume of interest (VOI) with a 40% isocontour around the valve on reconstructions that were provided

through a standardized calibration and reconstruction method by the European Association of Nuclear Medicine Research Ltd (EARL) when available(7). The target to background ratio (SUV_{ratio}) was then calculated as the ratio of the SUV_{max} of the valve and the SUV_{mean} of the blood pool in the descending aorta, not including the vessel wall. In all available cases, these measurements were also performed in non-EARL accredited reconstructions.

Additionally, extra-cardiac ^{18}F-FDG uptake was defined as either physiological, possible embolization, pathological lymph node or extra-cardiac infections/inflammation.

Cardiac CTA analysis

The CTA scans had been reported by a cardiac radiologist as part of clinical practice. We used the original clinical report to score for signs of infectious endocarditis (vegetations, mycotic aneurysms, abscesses, paravalvular leakage and valve dehiscence).

Statistics

For analysis of our main outcomes, descriptive statistics were used. Non-parametric statistical analyses (Mann Whitney-U test) were performed for the comparison of continuous variables in rejected and definite TAVI-IE. The interquartile ranges (IQR) and confidence intervals (CI) were denoted in square brackets. A significance level of p=0.05 and 95% CIs were used. In case of missing data, patients were excluded from analyses of certain parameters. SPSS statistics v24.0 (IBM Corp) was used for all analyses.

Follow-up

Information on patient follow-up was derived from the electronic patient records in each hospital. Follow-up time was defined as the period between the admission date until the date of the last notation in the clinical records. Data about mortality was derived from the Central Bureau for Statistics (CBS) database (100% available).

Results

Patient characteristics and classification

In total, 30 patients (mean age±SD 77±11; 17 males) with an initial suspicion of TAVI-IE were identified and included in this study. Valve types included 15 Corevalves, 8 Edwards Sapien and 7 others that, on average, had been implanted 278 days [104-768] (median with IQR) before ^{18}F-FDG-PET/CT imaging. Baseline patient characteristics are detailed in table 1. A detailed overview of all results per patient is given in Online Resource 1. Based on the modified Duke criteria 7/30 patients (23%) had the diagnosis of “definite TAVI-IE”, 22/30 patients (73%) “possible TAVI-IE” and 1/30 patients (3%) “rejected TAVI-IE”. After addition of ^{18}F-FDG-PET/CT and/or CTA, 12/30 patients (40%) had a final diagnosis of “definite TAVI-

Table 1: Patient characteristics

	All patients with suspicion of TAVI endocarditis	Definite TAVI endocarditis	Possible TAVI Endocarditis	Rejected TAVI endocarditis (after initial suspicion)
Demographics	n=30	n=12	n=12	n=6
Age, mean±SD, years	77±11	73±9	79±12	79±11
Gender, male, n(%)	17(57)	6(50)	7(58)	4(67)
BMI median[IQR], kg/m^2	26[23-32]	26[21-31]	25[23-30]	29[23-34]
Prior history of endocarditis, n(%)	0(0)	0(0)	1(8)	0(0)
Time since valve implantation, median[IQR], days	278[104-768]	116[60-699]	632[219-1451]	125[104-462]
Valves implanted <3 months prior to PET, n(%)	6(20)	4(13)	1(3)	1(3)
Type of valve, n(%)				
Corevalve	15(50)	5(42)	5(42)	5(83)
Sapien	8(29)	2(17)	5(42)	1(17)
Lotus	4(14)	4(33)	0(0)	0(0)
Portico	1(4)	0(0)	1(8)	0(0)
Directflow	2(8)	1(8)	1(8)	0(0)
Valve in valve TAVI, n(%)	0(0)	0(0)	0(0)	0(0)
Device, n(%)				
1 lead pacemaker	2(7)	0(0)	1(8)	1(17)
2 lead pacemaker	6(20)	2(17)	1(8)	3(50)
ICD/CRT-P/CRT-D	0(0)	0(0)	0(0)	0(0)
Blood cultures available, n(%)	30(100)	12(100)	12(100)	6(100)
Positive blood cultures, n(%)				
E. faecalis	12(40)	4(33)	5(42)	3(50)
Streptococci	8(27)	3(25)	5(42)	0(0)
S. aureus	2(7)	2(17)	0(0)	0(0)
S. lugudensis	2(7)	1(8)	0(0)	1(17)
S. epidermidis	2(7)	1(8)	0(0)	1(17)
Mycobacterium abscessus	1(3)	0(0)	0(0)	1(17)
Lactobacillus rhamnosus	1(3)	0(0)	1(8)	0(0)
Negative blood cultures	2(7)	1(8)	1(8)	0(0)
Days of IV antibiotic therapy prior to ^{18}F-FDG-PET/CT, median[IQR]	9[7-14]	10[7-14]	8[6-14]	11[7-25]
CRP* †, median[IQR], mg/L	47[15-106]	35[10-57]	86[26-149]	28[8-145]
Leukocytes* †, median[IQR], ×109/L	8.5[6.3-11.7]	7.5[6.3-11.7]	10.3[7.6-13.9]	5.5[5.0-8.7]
Median follow up period[IQR] (days) ‡	481[116-1060]	760[119-1140]	793[149-1139]	123[91-252]
All-cause mortality, n(%)	14(47)	6(50)	4(33)	4(67)

*CRP and leucocytes levels on the day closest to the 18F-FDG-PET/CT date were selected.
† In one patient the level of CRP and in 2 patients the level of CRP and Leucocytes prior to the 18F-FDG-PET/CT scan were missing. These patients were excluded from these analyses.
‡The numbers were derived from the most recent notes in the electronic patient files.

IE" based on Endocarditis Team consensus, whereas in 6/30 patients (20%) the diagnosis of endocarditis was rejected after additional diagnostic workup. In the remaining 12/30 patients (40%), the diagnosis of "possible TAVI-IE" was concluded. These patients were assigned and treated as "definite TAVI-IE". Overall, 10 patients (33%) were reclassified as

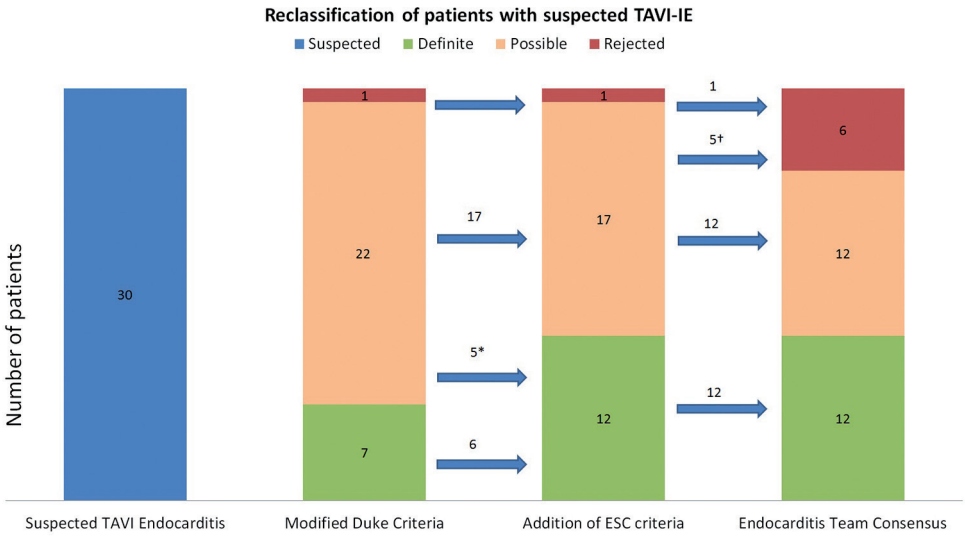

Fig. 1: Distribution of patients with suspected Endocarditis based on Modified Duke Criteria, ESC-criteria, and Endocarditis Team consensus based on ESC-criteria

detailed in Fig. 1. None of the patients underwent surgery. During a median follow-up of 481 [116-1060] days mortality was observed in 14/30 patients, including 6/12 patients with definite endocarditis, 4/12 possible and 4/6 rejected endocarditis.

Blood cultures

Blood culture results were available for all patients and were positive in at least once in 29/30 patients. *Enterococcus faecalis* was the most common type of micro-organism in patients with a final diagnosis of "definite TAVI-IE" (4/12) and those with "rejected TAVI-IE" (3/6).

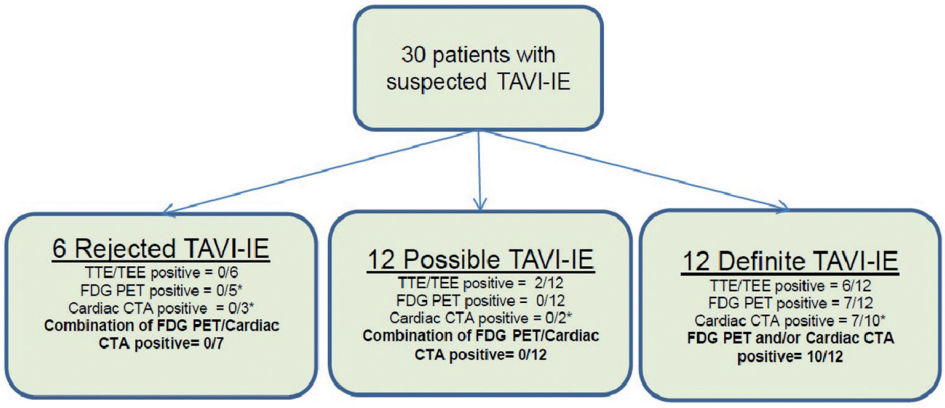

Fig. 2: Positive results of either TTE/TEE, FDG PET and Cardiac CTA in each group with final diagnosis of rejected, possible and definite TAVI-IE.

Echocardiography

The reports of TTE and/or TEE were available in all cases. TTE and/or TEE was positive in 6/12 patients with a final diagnosis of "definite TAVI-IE" and in 2/12 patients with "possible TAVI-IE" (1 with negative blood cultures and 1 with positive blood cultures but not meeting the major ESC criteria). In the "rejected TAVI-IE" group TTE and TEE were negative in all cases.

^{18}F-FDG-PET/CT

Visual analysis

^{18}F-FDG-PET/CT was performed in all patients. All scans were available for further quantitative analyses except one which could not be analysed quantitatively due to technical difficulties. The "time since implantation", "the days of antibiotic therapy prior to the scan" and "serum levels of CRP and leucocytes" were not significantly different between positive- and negative reported ^{18}F-FDG-PET/CT scans (table 2).

^{18}F-FDG-PET/CT was reported positive in 7 patients that all had a diagnosis of "definite TAVI-IE" (58%) (Fig. 3a-e). In all cases of "possible TAVI-IE" (n=12) and "rejected TAVI-IE" (n=6) ^{18}F-FDG-PET/CT was reported as negative. Additionally, a negative ^{18}F-FDG-PET/CT report was given in 5/12 patients with "definite TAVI-IE" (42%), including 2 with very low CRP levels (<10mg/L), 2 with moderate cardiac suppression due to high serum glucose levels during the scan (>10mmol/L) and 1 with no signs of endocarditis on any of the imaging modalities but a final diagnosis of definite TAVI-IE (positive blood cultures, prosthetic heart valve, fever and cerebral embolization).

Extra cardiac ^{18}F-FDG uptake was noticed in 19 patients, including 9 patients with a final diagnosis of definite TAVI-IE. Five patients were reclassified as rejected TAVI-IE after the ^{18}F-FDG-PET/CT demonstrated abnormal ^{18}F-FDG uptake elsewhere in the body indicating

Table 2: Time-interval from implantation, infection parameters, days of iv-antibiotic therapy, SUV_{max} and SUV_{ratio} around the prosthetic valve prior to ^{18}F-FDG-PET/CT in patients with a positive reported and negative reported ^{18}F-FDG-PET/CT scan.

	Positive reported ^{18}F-FDG-PET/CT	**Negative reported ^{18}F-FDG-PET/CT**
Time since valve implantation, median[IQR], days	126[76-557]	393[105-1212], p=0.29*
CRP, median[IQR], mg/L	25[11-53]	62[18-127], p=0.15*
Leukocytes, median[IQR], ×109/L	8.0[7.0-11.0]	9.6[6.0-12.5], p=0.63*
Days of IV antibiotic therapy prior to ^{18}F-FDG-PET/CT, median[IQR]	10[9-14]	9[7-14], p=0.48*
SUVmax, median[IQR]	5.5[3.8-7.1]	3.6[3.4-4.4], p=0.01*
SUVratio, median[IQR]	2.9[2.0-3.7]	1.9[1.7-2.1], p=0.04*

*Comparison between positive reported and negative reported 18F-FDG-PET/CT groups.

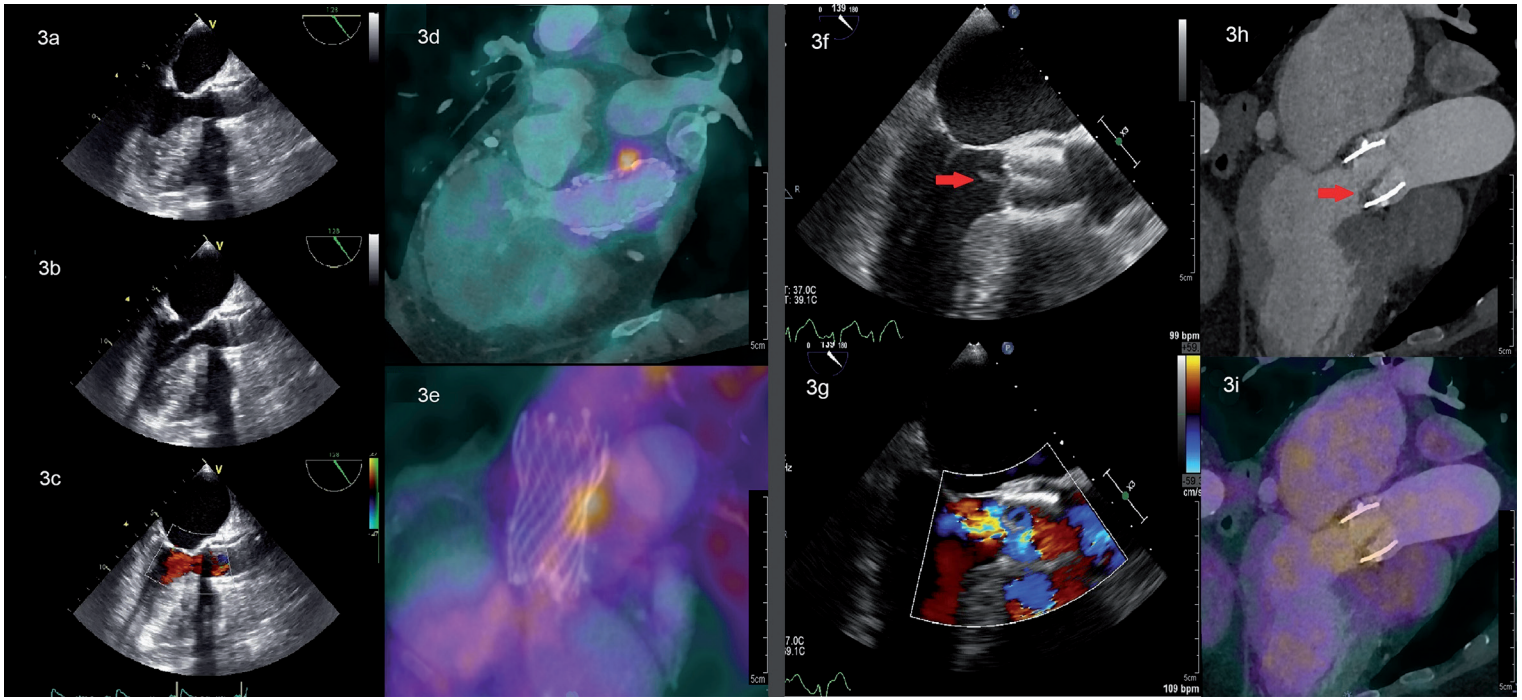

Fig. 3: Two cases of one positive PET/CT and one negative PET/CT for TAVI-IE. Case 1 (3a-3e): A 75-years old female with suspected Corevalve TAVI-IE who underwent a TEE without signs of endocarditis (3a-c). PET/CT images (3d/3e) demonstrated focal FDG uptake alongside the corevalve as positive sign of TAVI-IE. This case was previously published as a case report(14). Case 2 (3f-3i): An 81-years old female with suspected Edwards-Sapien TAVI-IE who underwent a TEE (3f/3g) with a vegetation on the aortic valve and mild aortic regurgitation. CTA demonstrated thickening of the aortic valve leaflets (3h) as possible signs of vegetation. However, PET/CT images (3i) showed no focal ^{18}F-FDG uptake on the leaflets. This was explained by the low inflammatory activity and 2 weeks of intravenous antibiotic therapy prior to the PET/CT scan.

an alternative infection that explained the clinical symptoms (without any signs of it being a septic embolic complication of endocarditis).

Quantitative analysis

EARL-reconstruction images were available in 20/30 (67%) of the cases and non-EARL-reconstruction images in 29/30 patients for further quantitative analyses. For both EARL and non-EARL standardized scans the SUV_{max} and SUV_{ratio} did not differ significantly between patients with definite TAVI-IE and rejected TAVI-IE. These SUV measurements are described in detail in table 3.

There was a significant difference between the SUV_{max} and SUV_{ratio} measured in the positive reported ^{18}F-FDG-PET/CT scans compared to the negative reported ^{18}F-FDG-PET/CT scans.

Table 3: SUV_{max} and SUV_{ratio} on the 18F-FDG-PET/CT scans for patients with definite-, possible- and rejected TAVI-IE.

	Definite TAVI-IE	Possible TAVI-IE	Rejected TAVI-IE
All EARL standardized scans	n=8	n=7	n=5
SUV_{max}, median[IQR]	3.6[2.8-4.8]	3.3[3.1-3.8]	3.6[3.3-3.9] P=0,83*
SUV_{ratio}, median[IQR]	2.0[1.7-2.2]	1.9[1.5-2.1]	1.7[1.3-2.3] P=0,38*
Non-EARL standardized scans	n=12	n=11	n=6
SUV_{max}, median[IQR]	4.1[3.5-5.8]	3.5[3.2-3.8]	4.2[3.4-4.5] P=0.85*
SUV_{ratio}, median[IQR]	2.3[1.7-2.9]	2.0[1.7-2.1]	1.9[1.8-2.3] P=0.40*

* Comparison of “definite TAVI-IE” and “rejected TAVI-IE” groups.

CT Angiography

Cardiac CTA was performed in 14/30 patients (47%) including 9/12 patients with definite-, 2/12 possible- and 3/6 rejected TAVI-IE. Positive signs of endocarditis such as vegetation (n=5), mycotic aneurysm (n=1) and both vegetation and mycotic aneurysm (n=1) were noticed in 7/9 (78%) patients with “definite TAVI-IE” (CTA not performed in 3/12 patients with definite endocarditis). The other 2/9 patients with definite TAVI-IE but negative CTA, either had positive signs of TAVI-IE on the ^{18}F-FDG-PET/CT (1/2) or TTE/TEE (1/2). Three out of 7 patients with a positive CTA had no signs of endocarditis on the TTE/TEE. The mycotic aneurysms detected in 2 cases on CTA were not visible on TTE/TEE.

Impact of ^{18}F-FDG-PET/CT and CTA

^{18}F-FDG-PET/CT helped to reclassify 8 patients from the initial possible TAVI-IE group to either the definite TAVI-IE group (3/8) or the rejected TAVI-IE group (5/8). Additionally, CTA aided in the reclassification of an additional 2 patients that had a normal ^{18}F-FDG-PET/CT by identifying vegetations or other structural abnormalities, while strengthening the reclassification by ^{18}F-FDG-PET/CT in 4 patients by also depicting structural abnormalities

when increased ^{18}F-FDG uptake had already been identified. Details of reclassification and number of imaging techniques used in each group are demonstrated in Fig. 1 and Fig. 2.

Discussion

In daily clinical practice, patients with a prosthetic valve who show signs of unexplained infection and develop positive blood cultures are highly suspected for endocarditis. Even if echocardiography does not show any signs of endocarditis, these patients may be pragmatically treated as such, however this has major clinical implications. If ^{18}F-FDG-PET/CT shows signs of infection elsewhere without any signs of endocarditis, this may lead to a change in diagnosis and reduction of the antibiotic treatment period. On the other hand, if the diagnosis is changed to definite endocarditis due to the ^{18}F-FDG-PET/CT findings, the antibiotic treatment may be prolonged or even adjusted to lifelong suppression therapy. All these changes might have effects on morbidity and mortality.

Our study showed that the use of ^{18}F-FDG-PET/CT and/or CTA resulted in reclassification of 10/22 (45%) patients with an initial diagnosis of "possible TAVI-IE". Furthermore, the addition of ^{18}F-FDG-PET/CT led to alternative diagnoses in 4 patients initially suspected of TAVI-IE. CTA was not performed in all patients (14/30, 47%), but was positive for signs of TAVI-IE in a substantial number of patients with the final diagnosis of "definite TAVI-IE" (7/9; 78%) by demonstrating vegetations and/or mycotic aneurysms that were not seen on TTE/TEE (4/9; 44%) (Fig. 4).

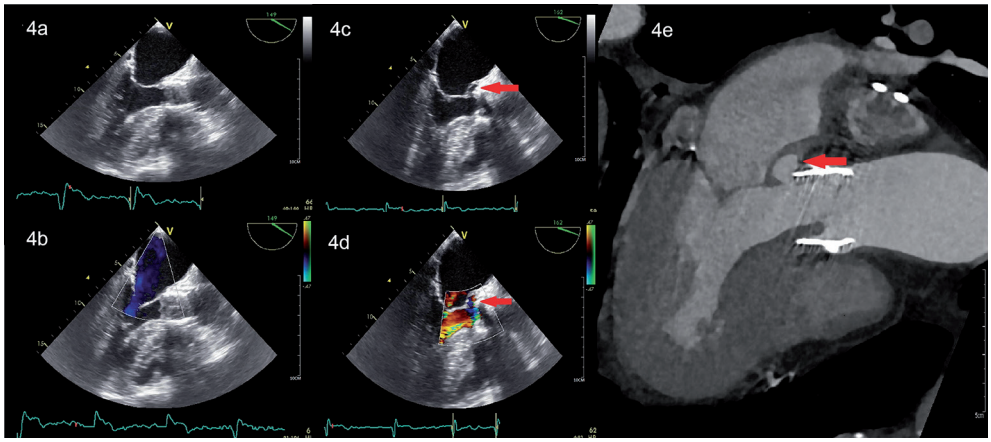

Fig. 4: CTA images of a 77-years old male with suspected TAVI-IE. Initial TEE (4a-4b) showed only thickened aortic valve leaflets as signs of vegetation. Repeating TEE after a few days (4c-4d) showed a new aortic regurgitation and a paravalvular space as sign of possible mycotic aneurysm, which was confirmed on the CTA (4e).

Although we did not encounter them in this study, false positive ^{18}F-FDG-PET/CT results can occur in PVE and therefore cautious interpretation of ^{18}F-FDG-PET/CT scans is advised, particularly taking into account the known confounders (7, 12). Potentially, chronic inflammation and thus false ^{18}F-FDG uptake might also be caused by continuous movement and friction of the transcatheter implanted valve. Moreover, the presence of calcifications on the native aortic valve, which are not removed during a TAVI procedure, may cause artefacts and thus false positive ^{18}F-FDG-PET/CT results. Overcorrection of the ^{18}F-FDG uptake signal inside the valve ring may occur during the attenuation correction (AC) due to (artefacts coming from) the metal stent around the TAVI prosthesis, necessitating side-by-side interpretation of AC and non-AC images. In a recent large study of patients suspected of PVE (including TAVI-IE), recent valve implantation was not found to be a significant predictor of a false positive ^{18}F-FDG-PET/CT scan(6). In addition, the inflammation response caused by percutaneously implanted valves may even be less compared to surgically implanted valves.

False negative ^{18}F-FDG-PET/CT results can occur due to negative confounding effects such as low inflammatory activity caused by antibiotic treatment before the ^{18}F-FDG PET/CT(6, 14) (Fig. 3f-i).

The standardization of calibration and reconstruction method between centers remains challenging and EARL reconstruction are not formally recommended for cardiac purposes. In our study we performed the quantitative analysis on both the EARL- as well as the non-EARL reconstruction images and on both analyses, we did not find a statistically significant difference between the rejected TAVI-IE and the definite TAVI-IE groups.

In a recent study quantitative assessment of ^{18}F-FDG-PET/CT after exclusion of significant confounders produced cut-off values with good diagnostic accuracy(6). Our results did not corroborate these findings in TAVI-IE (Table 3). Comparing our results to the earlier study, ^{18}F-FDG-PET/CT seems more likely to underdiagnose TAVI-IE than PVE in general, although we must be cautious in generalizing our findings. Our study contained 5 patients with a false negative ^{18}F-FDG-PET/CT scan, who had signs of a vegetation on either CTA (2/5), TTE/TEE (1/5) or both (1/5). This underlines the value of anatomic imaging with CTA and echocardiography (on top of metabolic imaging) in order to detect vegetations which may easily be missed by ^{18}F-FDG-PET/CT due to the low inflammatory response associated with vegetations.

It is important to be aware of potential pitfalls when interpreting valvular abnormalities on CTA. Prosthetic stent material induced artefacts may obscure valvular abnormality and cause false negative results. On the other hand, leaflet thrombosis (hypo attenuating leaflet thickening, HALT) can occur after TAVI even when patients use anticoagulation therapy(15, 16). HALT may potentially be misinterpreted as a vegetation and lead to false positive CTA

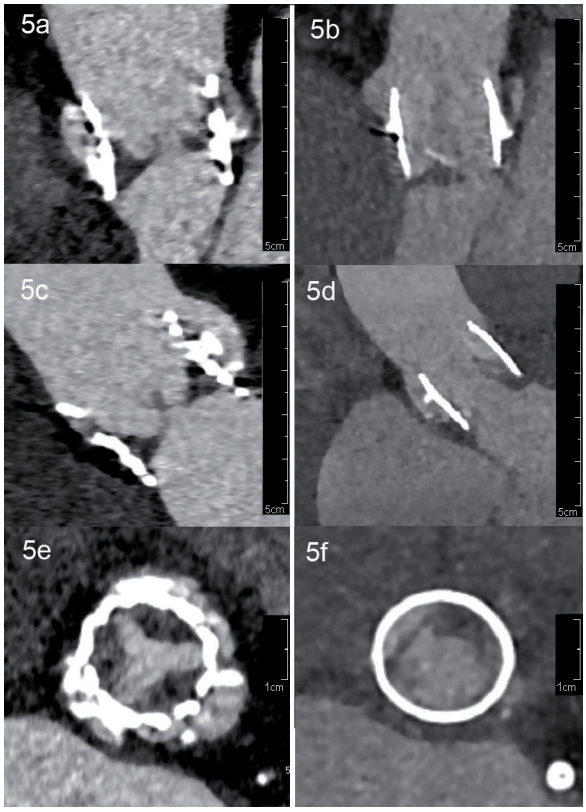

Fig. 5: CTA images of a Sapiens valve with signs of leaflet thrombosis (5a,c,e) and a Lotus valve with signs of vegetation (5b,d,f).

findings. Besides the clinical context, HALT tends to be located at the base of the leaflets and taper toward the free edge, whereas vegetations have a more irregular shape and can be much larger (Fig. 5).

The value of ^{18}F-FDG-PET/CT and cardiac CTA in the diagnosis of TAVI-IE was, besides case reports (13), only shown once before in a recently published case series of 16 patients(9). It showed significant potential of this multi-imaging approach and suggested the use of ESC-criteria for the diagnosis of TAVI-IE. Our results confirm these findings. Moreover, our study demonstrates the additional diagnostic value of ^{18}F-FDG-PET/CT and CTA for patients suspected for TAVI-IE. It results in a change of the final diagnosis when the ESC criteria are applied instead of the modified Duke criteria alone and supports a more widely use of these relatively new techniques.

All mentioned imaging techniques seem to have additional diagnostic value. Although the newer imaging techniques are expensive and associated with some radiation, they provide important extra information allowing a better diagnostic process, which is crucial for these seriously ill patients.

There are several limitations to our study. The most important is the way the final diagnosis was established. Since no patient had undergone surgery, we relied on the ESC criteria and the decision of the Endocarditis Team for the final diagnosis. Since ^{18}F-FDG-PET/CT and CTA results were taken into account when making the decision for the final diagnosis, this can be seen as an incorporation bias and thus as a major limitation of this study. However, due to the retrospective design of the study, this could not readily have been prevented. This problem exists in most endocarditis studies as the pathological Duke criteria are often not available(3). Additionally, the retrospective nature of the study and relatively small number of patients limit the generalization of our findings to all patients with TAVI-IE.

In conclusion, the addition of ^{18}F-FDG-PET/CT and CTA in the work up of patients with suspected TAVI-IE provided valuable complementary information to echocardiography resulting in reclassification of 33% of patients in our study.

New Knowledge Gained

^{18}F-FDG-PET/CT and CTA help clinicians to assess patients with TAVI-IE and both of these imaging tools should be considered in the diagnostic work-up of patients with suspected TAVI-IE.

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PART IV

The Value of Cardiac CT in the Diagnosis of Infective Endocarditis

Chapter 9

Screening for coronary artery disease in early surgical treatment of acute aortic valve infective endocarditis

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Abstract

Objective: In patients with unknown coronary status undergoing surgery for acute infective endocarditis (IE), the need to screen for coronary artery disease (CAD) and the risk of embolization during invasive coronary angiography (ICA) are debated. Coronary computed tomography angiography (CCTA) is a non-invasive alternative in these patients. We aimed to evaluate the safety and feasibility of ICA and CCTA to diagnose CAD, and the necessity to treat CAD to prevent CAD related postoperative complications.

Methods: In this single center retrospective cohort study, all patients with acute aortic IE between 2009-2019 undergoing surgery were selected. Outcomes were any clinically evident embolization after preoperative ICA, in-hospital mortality, perioperative myocardial infarction or unplanned revascularization and postoperative renal function.

Results: Of the 159 included patients, CAD status was already known in 14. No preoperative diagnostics for CAD was done in 46/145, a CCTA was performed in 54/145 patients and an ICA in 52/145 patients. Significant CAD was found after CCTA in 22% and after ICA in 21% of patients. In 1 of the 52 (2%) patients undergoing preoperative ICA a cerebral embolism occurred. The rate of perioperative myocardial infarction or unplanned revascularization in patients not screened for CAD was 2% (1 out of 46 patients).

Conclusions: Although the risk of embolism after preoperative ICA is low, it should be carefully weighed against the estimated risk of CAD-related perioperative complications. CCTA can serve as a gatekeeper for ICA in most patients with acute aortic IE.

Introduction

Acute infective endocarditis (IE) is associated with high rates of morbidity and an in-hospital mortality of approximately 17-20%[1, 2]. Early surgical treatment is often indicated[2]. The indications are mainly related to the presence of uncontrolled infection despite adequate antimicrobial treatment or hemodynamic deterioration[3].

Because treating concomitant coronary artery disease (CAD) at the time of aortic valve replacement improves outcome, CAD-screening is part of the preoperative workup[4]. To this end, an invasive coronary angiography (ICA) is performed in most IE patients scheduled for surgery[5]. There remains discussion about the safety of ICA in patients with IE, especially in those with large aortic valve vegetations. Catheter manipulations in the aortic root may dislodge infectious tissue and cause embolization[6]. Previous studies suggested that ICA might be safe in patients with acute IE, even in the presence of vegetations[5, 7, 8]. However, since not all studies were methodologically adequate to evaluate safety, not enough data is available to conclude that ICA is safe in patients with aortic valve IE and vegetations, especially those larger than 10mm. Furthermore, these studies did not evaluate the use of coronary computed tomography angiography (CCTA), a non-invasive alternative to ICA[9, 10]. These uncertainties cause variability in diagnosis and management of CAD in IE patients being considered for aortic valve surgery. We aimed to evaluate the prevalence of CAD in patients with acute IE of the aortic valve, the safety and feasibility of ICA and CCTA for diagnosis of CAD, and the necessity to treat CAD to prevent CAD related postoperative complications.

Methods

The local institutional review board approved our study (MEC-2019-0125) and the need for informed consent was waived. The study adhered to the STROBE guidelines[11].

Study population

Out of 267 consecutive patients that presented to the Erasmus Medical Center in Rotterdam between 2009-2019 with definite IE of the aortic valve according to the 2015 European Society of Cardiology (ESC) modified criteria [3], all patients were selected that underwent surgical treatment during the acute phase of the disease. Both native and prosthetic aortic valve IE were included. The acute phase was defined as surgery during the initial period of antibiotic treatment, positive tissue cultures or pathological examination indicating active infection. To prevent missing any potential patients in which surgery was canceled due to complications related to ICA, all 267 patients including those that did not undergo surgery, were screened for embolic events.

Data collection

Data was collected on the type, duration and severity of IE, modalities used to diagnose CAD, coronary artery disease status, surgical records and in-hospital outcomes. The coronary status was regarded as known when an ICA or CCTA was available prior to the episode of endocarditis, within 12 months before the operation. CAD in this study was defined on a patient level as one or more anatomically significant lesions, following the clinical reports, with specific cut-off values for CCTA (>50% stenosis) and ICA (>50% stenosis in left main or >70% stenosis in other branches). CT-scans were only included as CCTA if the acquisition followed a protocol aiming for reliable evaluation of the coronary arteries. Scans were scored as not assessable only when one or more coronary arteries were not assessable due to artefacts or poor image quality due to other reasons, and when the remaining arteries were free of CAD. Scans where at least one coronary artery showed a stenosis and image quality of one or more other coronary arteries was poor were scored as CAD positive. The decision to perform preoperative screening was at the discretion of the heart team (comprising at least a cardiac surgeon and a cardiologist, prior to 2016) or the 'endocarditis' team (comprising among others a cardiac surgeon, a cardiologist and a radiologist, from 2016 onwards). Outcomes were in-hospital mortality, embolization after ICA, a combination of perioperative myocardial infarction and/or in-hospital perioperative unplanned coronary revascularization, and renal failure. To evaluate adverse effects of ICA and CCTA on renal function, renal function was collected at three points in time: at hospital admission, the lowest postoperative filtration rate and at discharge. Renal function was categorized as a glomerular filtration rate of <30, 30-60 or >60 ml/min/1,73m^2 using the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation[12]. Perioperative unplanned coronary revascularization included any concomitant coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) that was not planned prior to the start of surgery. Embolization after ICA was defined as any embolic event within 24 hours after ICA or until the start of surgery, whatever came first. A full list of relevant definitions can be found in Supplementary Table S1.

Statistical analysis

Categorical data were summarized by frequencies and percentages and were compared using the "Chi-squared" or "Fisher's exact" test. To compare age and EuroSCORE II between the subgroups an "ANOVA test" was used. When the omnibus test indicated significance, no further in-between group testing was performed. To compare incidence of renal failure after both imaging modalities, patients that underwent either one or both, were split into groups with a CCTA first or direct ICA approach. Both the renal function and decrease in renal function were analyzed within the aforementioned categories (eGFR >60, 30-60 or <30 ml/min/1,73m^2). The changes in renal function after surgery and at discharge were tested using the "Mann-Whitney U" test. Statistical analyses were performed using SPSS software version 25 (SPSS Inc, Chicago, Illinois).

Results

Study population

A total of 267 consecutive patients presented to our hospital with definite IE of the aortic valve. Our eventual study group consisted of the 159 patients that underwent surgery during the active phase of the infection; 63% (n=100) with native valve IE and 37% (n=59) with prosthetic valve IE. Baseline characteristics of the study population and a comparison of baseline differences among subgroups, based on the screening approach, can be found in table 1. In table 2 the data on IE is presented. A flowchart of the study population is shown in Figure 1.

Coronary artery disease

Of the 159 patients, coronary artery disease status was known prior to the diagnosis of endocarditis in only 14 patients (9%). In these patients, there was no significant CAD or the patient was already treated prior to presentation with IE. In the patients with unknown CAD status, no preoperative diagnostics for CAD was performed in 46 patients (32%), CCTA was performed in 54 patients (37%) and ICA in 52 patients (36%). All diagnostic results are shown in table 3.

In 2 (4%) of the 54 CT-scans, CAD could not be ruled out because at least one of the coronary arteries was not assessable. CAD was ruled out in 40 patients (74%), while significant CAD was found in 12 patients (22%). In seven patients (5% of study population, 13% of patients with CCTA-first approach) an ICA was performed after CCTA, to confirm CAD (n=4), because of high risk of CAD(n=2) or non-assessable CCTA (n=1). Of the four patients with positive CT-scan, ICA was positive in two patients. Average age of patients with vs. without need for downstream ICA after CCTA, was 66.1 vs 58.4 years (p=0.13).

In 21% (11/52) of patients that underwent ICA at least one significant coronary artery stenosis was detected. Four of these patients underwent direct PCI, either due to an initial presentation of endocarditis with an acute coronary syndrome (n=3) or because of a known lack of suitable venous material for CABG (n=1). An FFR value was measured in only two patients, both of which were negative. Overall, excluding the two false-positive CCTA's, CAD was present in 12% (n=19) of the patients screened by CT or ICA in our study.

Surgery

All patients underwent replacement of the infected aortic valve. Operative characteristics are summarized in table 4 and Supplementary Table S2. Concomitant CABG was planned in 5 patients, all of which underwent preoperative ICA. In these patients, significant stenoses were found in three, whereas intermediate lesions were treated in the other two. Based on preoperative imaging, CAD was not treated invasively in any of the eight patients diagnosed

Table 1: Baseline characteristics of study population and of subgroups

	All patients (n=159)	No diagnostics (n=46)	CAD status known (n=14)	Initially CT-group (n=54)	Initially ICA-group (n=45)	p-value
Sex (male), % (n)	79 (123)	70 (32)	86 (12)	87 (47)	78 (35)	0.17
Age (in years)	58 (SD: 15)	49 (SD: 19)	62 (SD: 14)	59 (SD: 13)	66 (SD: 9)	<0.001
Hypertension, % (n)	43 (68)	33 (15)	50 (7)	46 (25)	47 (21)	0.43
Diabetes, % (n)						
Oral medication	9 (15)	13 (6)	21 (3)	4 (2)	9 (4)	0.11
On insulin	2 (3)	2 (1)	7 (1)	2 (1)	0	
Dyslipidemia	33 (52)	28 (13)	50 (7)	26 (14)	40 (18)	0.21
Obesity	13 (20)	13 (6)	14 (2)	11 (6)	13 (6)	0.98
Smoking history, % (n)						
Yes	33 (53)	20 (9)	29 (4)	37 (20)	44 (20)	0.12
Unknown	10 (16)	7 (3)	14 (2)	11 (6)	11 (5)	
Peripheral vascular disease, % (n)	7 (11)	2 (1)	14 (2)	7 (4)	9 (4)	0.31
Prior revascularization, % (n)	8 (13)	0	21 (3)	4 (2)	18 (8)	0.001
Prior PCI, % (n)	4 (6)	0	7 (1)	0	11 (5)	0.006
Prior CABG, % (n)	4 (7)	0	14 (2)	4 (2)	7 (3)	0.068
Prior cardiac surgery, % (n)	40 (63)	52 (24)	71 (10)	30 (16)	29 (13)	0.004
(a)typical angina, % (n)	6 (10)	0	7 (1)	2 (1)	18 (8)	0.002
Left ventricular function, % (n)						
Normal (>50%)	4 (7)	87 (40)	71 (10)	91 (49)	62 (28)	0.007
Moderate (30-50%)	16 (25)	11 (5)	21 (3)	6 (3)	31 (14)	
Poor (<30%)	80 (127)	2 (1)	7 (1)	4 (2)	7 (3)	
EuroSCORE II [19]	13.39% (SD: 15.24)	16.78% (SD: 17.24)	20.86% (SD: 20.41)	9.41% (SD: 11,90)	12.38% (SD: 13.64)	0.020
Vegetation present Left ventricular function, % (n)	71 (113)	61 (28)	71 (10)	80 (43)	71 (32)	0.24
Vegetation >10 mm Left ventricular function, % (n)	37 (59)	28 (13)	29 (4)	46 (25)	38 (17)	0.32
Heart failure at time of presentation Left ventricular function, % (n)	58 (91)	48 (21)	71 (10)	54 (29)	69 (31)	0.11
Renal failure at time of presentation Left ventricular function, % (n)						
eGFR >60	28 (45)	65 (30)	57 (8)	61 (33)	53.3 (24)	0.22
eGFR 30-60	12 (19)	17 (8)	29 (4)	35 (19)	31 (14)	
eGFR <30	3 (5)	17 (8)	14 (2)	4 (2)	16 (7)	
Dialysis		0	14 (2)	0	7 (3)	0.008

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; ICA: invasive coronary angiography; PCI: percutaneous coronary intervention; SD: Standard Deviation.

Table 2: Endocarditis Characteristics

Pathology positive, % (n)	80 (127)
Type of IE	
Native, % (n)	63 (100)
Prosthetic, % (n)	37 (59)
Mechanical valve prosthesis:	
St Jude, % (n)	51 (30)
On-X, % (n)	2 (1)
Sorin Bicarbon, % (n)	2 (1)
Biological valve prosthesis:	
C-E Perimount, % (n)	25 (15)
C-E Perigon, % (n)	5 (3)
Homograft/autograft, % (n)	14 (8)
Transcatheter valve prosthesis, % (n)	2 (1)
Fever, % (n)	79 (125)
Vegetation, % (n)	71 (113)
Pathogen	
Viridans streptococcus, % (n)	40 (64)
S. Aureus, % (n)	13 (20)
Coagulase negative streptococcus, % (n)	9 (15)
Enterococcus, % (n)	7 (11)
Proprioni bacterium, % (n)	14 (22)
Culture negative, % (n)	4 (6)
Other, % (n)	13 (21)
Abscess/pseudo aneurysms, % (n)	35 (56)
Embolic event *	
Embolism, % (n)	40 (64)
Neuro-embolism, % (n)	17 (27)

* All patients with an embolic event observed during the period of infective endocarditis, either prior to presentation, or between presentation and surgery.

only by CCTA, in two patients with CAD diagnosed by ICA and in the two patients with CAD diagnosed by both ICA and CCTA.

In four patients it was decided during surgery to perform CABG. In three of these patients, this decision was based on ventricular failure, causing difficulties in weaning from extracorporeal bypass. In these cases, the surgeon presumed that the cause of the failure was ischemic. The other patient suffered a lesion to a graft from a previous CABG procedure, necessitating replacement.

Outcomes

One patient with an aortic vegetation >10mm suffered a cerebral stroke within 24 hours after undergoing a preoperative ICA procedure. No other embolization was witnessed after ICA, neither in the study population, nor in the patients treated conservatively and screened for ICA complications. Apart from this patient, incidence of embolic events

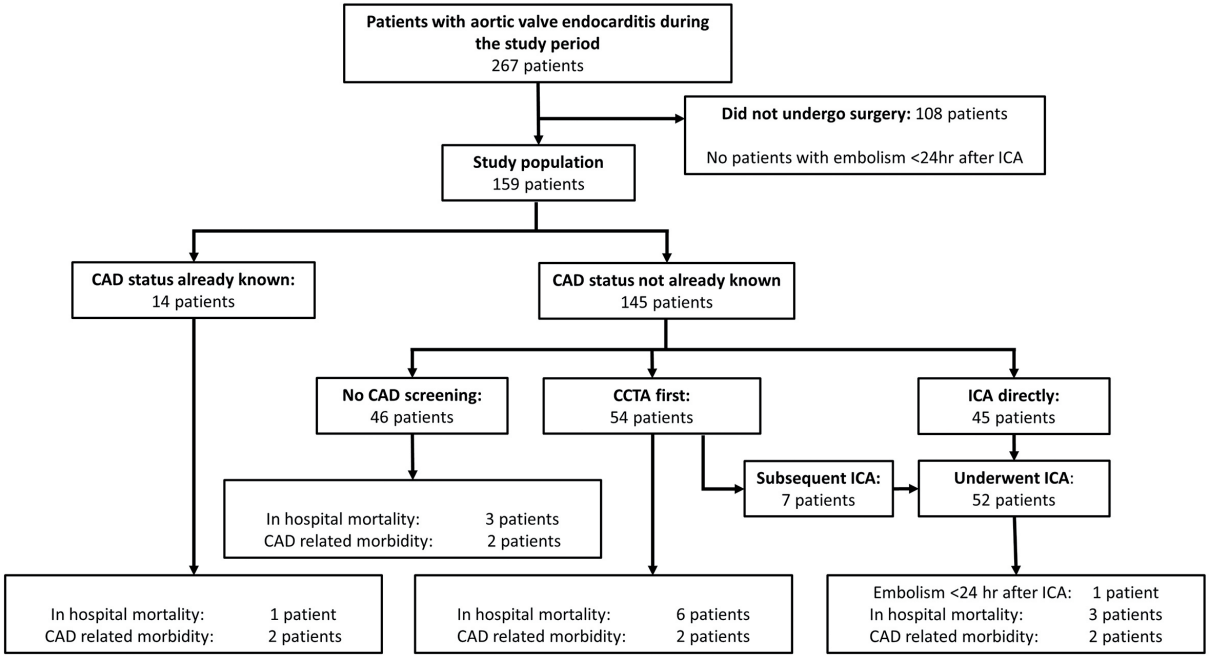

Figure 1 A flowchart of the study population

Table 3: Overview of CAD diagnostics

Diagnostics (of n=159) , % (n)	
Coronary status already known	9 (14)
No diagnostics preop, no known CAD status	29 (46)
CCTA	34 (54)
ICA	33 (52)
CCTA+ICA	4 (7)
CCTA (n=54) , % (n)	
Not assessable (1 or more arteries)	4 (2)
CAD excluded	74 (40)
CAD found	22 (12)
False positive (+CCTA vs ICA, patient level)	50 (2/4)
Vegetation present	80 (43)
Vegetation >10mm	46 (25)
CAD2 score clinical	15 (SD: 12.3 %)
ICA (n=52) , % (n)	
CAD excluded	79 (41)
CAD found	21 (11)
Vegetation present	71 (37)
Vegetation >10mm	37 (19)
CAD2 score clinical	21 (SD: 16.9 %)
FFR measured	4 (2)
CAD prevalence after screening [a]	12 (19)
CAD at time of surgery, % (n)	
CCTA positive [b]	5% (8)
ICA positive [b]	3% (5)
CCTA+ICA positive	1% (2)

a) In patients with preoperative screening with (true) positive CT or ICA (n=99)
b) not counting CCTA+ICA pts

Table 4: Operative characteristics

AVR, % (n)	100% (159)
Concomitant mitral valve surgery, % (n)	24% (38)
Concomitant aortic root surgery, % (n)	36% (57)
Cardiopulmonary bypass time (minutes)	187 (SD: 98)
Crossclamp time (minutes)	131 (SD: 63)
Concomitant CABG (planned) , % (n)	3% (5)
Concomitant CABG (performed) , % (n)	6% (9)
CAD either not present or treated, % (n)	
Yes	62% (99)
Unknown	30% (48)
CAD not treated during surgery, % (n)	
Of CCTA + lesions [a]	5% (8)
Of ICA+ lesions [a]	2% (2)
CCTA+ICA positive	1% (2)

a) not counting CCTA+ICA pts

Table 5: Outcomes

In-hospital mortality, % (n)	8% (13)
ICA embolism, % (n)	
Out of all patients	1% (1)
Out of ICA patients	2% (1)
Of ICA patients with vegetation	3% (1)
Of ICA pts with vegetation > 10mm	5% (1)
Perioperative myocardial infarction / unplanned revascularization, % (n)	
All patients	5% (8)
CAD already known status (n=14)	13% (2)
CAD unknown patients (n=46)	4% (2)
CCTA (n=54)	4% (2) (of which 1 CCTA positive)
ICA (n=52)	4% (2)

CAD: coronary artery disease; CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography.

between initiation of antimicrobial treatment and surgery was 5% (8 patients) in our study population. All outcomes are presented in table 5. In-hospital mortality was 8.2% (n=13). Perioperative myocardial infarction or unplanned revascularization was seen in 5% (n=8). In four of these patients (two with negative ICA, one with negative CT and one with unknown coronary status) the cause was most likely surgical (accidental injury of vein graft, stenosis of a coronary button, compression of valve prosthesis on an aberrant circumflex artery and possible coronary embolization). Two other patients with already known coronary status both underwent prior revascularization, which turned out to have been incomplete at the time of the surgery for IE. In one patient, the CCTA showed evidence of significant CAD, but patient proceeded to surgery before an ICA was performed because of hemodynamic deterioration. A postoperative ICA showed three vessel disease. In the last patient the CAD status was unknown at the time of surgery and he experienced ventricular failure, culminating in multi organ failure and death.

Renal failure

In the overall study population, the prevalence of renal failure with CKD stage 4 and 5 (eGFR <30) was 12% (n=19) at the time of presentation, 25% (n=39) shortly after surgery and 5% (n=8) at discharge. When comparing the CCTA first vs. ICA diagnostic approaches, differences were observed in neither absolute renal function, nor in the postoperative change in renal function. Figure 2 shows the renal function of these groups before and after surgery. Supplementary Table S3 contains all data on renal failure.

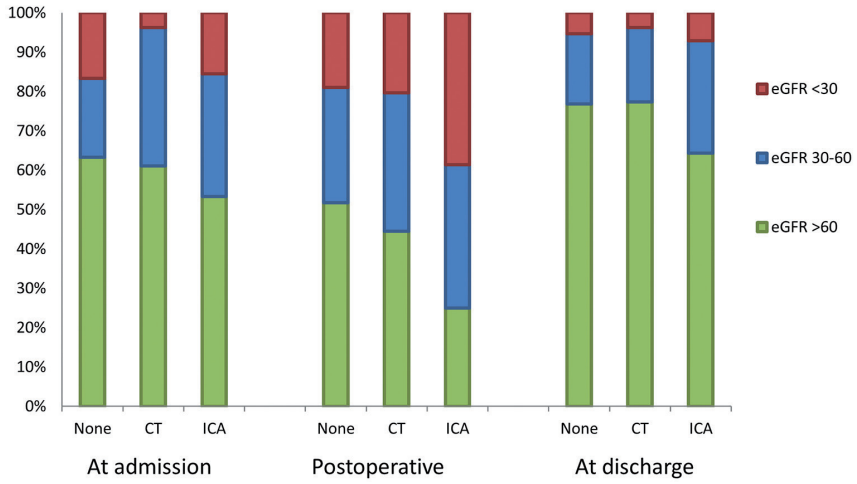

Figure 2: Renal function at time of admission, the lowest renal function postoperatively and at discharge.

Discussion

In our study population of patients with active aortic valve IE, we have observed one patient that suffered a cerebral embolism after a preoperative ICA. No preoperative diagnostics for CAD was done in 46/145, a CCTA was performed in 54/145 patients and an ICA in 52/145 patients. Significant CAD was found after CCTA in 22% and after ICA in 21% of patients. Even though just a minority of patients with CAD was treated with concomitant CABG, only one patient with known but untreated CAD needed unplanned revascularization postoperatively.

Safety of ICA

Safety of ICA in patients with active aortic valve IE has long been a topic of discussion. Both the ESC and American College of Cardiology/American Heart Association guidelines on IE recommend performing an ICA in all patients with at least one cardiovascular risk factor, patients with a history of coronary artery disease, male patients >40 years of age and post-menopausal women[3, 13]. An exception is made for patients with aortic vegetations that may be dislodged, although this is not further specified. In general, risk of embolization of a vegetation depends largely on its length, with >10mm being a frequently used cut-off[14]. Embolic events caused by ICA have only been described in one case report, where a patient with an aortic valve vegetation of 13 mm suffered from a fatal septic embolism to the left main coronary artery after preoperative ICA. Since then, small cohorts of patients with mitral or aortic valve IE undergoing ICA have been described without occurrence of embolization[8]. These studies frequently include only patients that were operated on, a methodological error that by design overlooks patients that might have suffered severe

morbidity after preoperative ICA, precluding surgery. One recent study did report on 86 patients with aortic valve IE undergoing preoperative ICA, in 49 of which an aortic vegetation was observed[5]. Size of the vegetation was not reported. No embolic events were observed, leaving the authors with the conclusion that ICA is a safe procedure in patients with IE. In our study however, evaluating only patients with aortic valve IE, we have found one patient with a stroke within 24 hours after ICA. Of course, it is impossible to determine whether this stroke was indeed caused by manipulation of the vegetation. Also, since only one event was observed, an absolute risk cannot be estimated. In our patient, the vegetation was also large (14mm). The risk of embolization most likely depends on the location, size and mobility of the vegetation, and the physician awareness of the vegetation. In cases where presence of an aortic vegetation is known, a more careful approach can be used with regard to wire handling and contrast injection. Based on the results of this and previous studies, this leads to a low, but non-negligible risk of embolization in patients with aortic valve vegetations undergoing ICA.

Computed tomography to rule out coronary artery disease

Based on our and previous studies, the risk of CAD seems to be lower in patients with IE, when compared to the CAD incidence of approximately 40% in patients with ordinary valvular heart disease[5, 15, 16]. This might be associated with age. Another explanation is that patients with ordinary valvular disease are more prone to have atherosclerosis. In patients with low to intermediate risk of CAD, CCTA is an excellent non-invasive imaging modality to rule out significant stenosis[10]. To date, our study has the largest population of patients with active aortic IE being screened for CAD using CCTA. Results of the CCTA agreed with ICA in five patients and was false positive in two. Despite the highly selected patient sample, this reflects the high sensitivity but moderate specificity and positive predictive value of CCTA. CCTA was not assessable on a patient level in only 4% (n=2). Despite a state of active infection and possible tachycardia, CCTA seems to be of adequate diagnostic quality in most patients, to effectively rule out significant CAD. Because of the low positive predictive value, contemporary CCTA imaging is not suited to guide treatment. Therefore, it can only be used as a gatekeeper for ICA, with a negative CCTA deferring the need for ICA.

Clinical perspective

Choosing for a CCTA first approach will eventually decrease the need for invasive testing and the associated risks thereof. In addition, it can provide important additional information on potential cardiac anatomic abnormalities related to IE, such as abscesses or mycotic aneurysms.[17] This will however come at a cost of an increasing burden of contrast agents, fluid volume and radiation dose in patients where the CCTA cannot rule out CAD. This is of special concern in patients with active IE owing to the higher risk of heart failure, renal failure and possibly also a higher risk of inadequate image quality of the CCTA due to tachycardia. In our study we have found adequate image quality in the vast majority of

patients, a theoretical need for downstream ICA in 26% of patients after CCTA and we found no evidence of an adverse effect of the CCTA first approach on the renal function either in the decline shortly after surgery or at time of discharge. Adequate patient selection is critical. In patients with low or intermediate risk of CAD, especially those with aortic vegetations, a CCTA first approach can rule out CAD in a majority of the patients. Performing an ICA directly in patients with high risk of CAD, such as older patients with multiple risk factors or patients with chronic kidney disease, seems to be associated with a low risk of embolization, even despite the presence of aortic vegetations. Because of poor diagnostic quality of CCTA in patients with certain older types of mechanical valve prosthesis, especially those with cobalt-chrome, ICA should be favored in these patients[18].

Necessity of treating concomitant coronary artery disease

In a recent retrospective study in patients undergoing surgery for active or treated left sided IE, 73% of patients with CAD found on preoperative ICA did not undergo concomitant CABG[16]. Even though outcomes were not compared to patients with concomitant CABG, the authors concluded that ICA might be overused in patients with IE. They argued that only 9% of patients that underwent ICA received CABG, and that 30-day mortality was similar in patients with or without preoperative ICA. In the study by Laperche et al 38% (n=15) of patients with an indication for concomitant CABG were not treated[5]. None of them suffered from perioperative myocardial infarction or needed revascularization. In our study 80% (n=12) of CAD positive patients did not undergo CABG or PCI. One of these patients needed urgent revascularization postoperatively. Most of the other patients deferred from CABG, had an isolated stenosis in a diagonal branch or right coronary artery and revascularization was deemed less opportune. It is important to note that many patients with active IE in whom CAD is found by preoperative screening are asymptomatic. The results of our and previous studies might suggest that, especially in cases of modest severity, CABG might safely be deferred in some patients with CAD, based on heart team consensus. However, selection bias has to be taken into account, and therefore more reliable data is needed to more precisely estimate the risk of adverse outcome when deferring CAD treatment in patients with active IE. Furthermore, safe deferral of CABG in these patients does not mean that CAD screening is unnecessary. In our study the rate of perioperative myocardial infarction or unplanned revascularization in patients not screened preoperatively for CAD was 6% (4/60). All four patients had an indication for ICA screening according to the guidelines[3, 13]. This finding is not in line with the conclusion of previous studies that CAD screening is over utilized in patients with IE[16].

Limitations

Our study has several limitations. It is a retrospective study and selection of different approaches in diagnosing and treating CAD were very dependent on patient characteristics. IE has a variable disease presentation and our study population is very heterogeneous.

Because of these limitations, we have refrained from statistical inference between groups with different screening approaches to compare outcomes of screening and surgery. The only exception is the analysis of renal failure, because we believe that this is less prone to selection bias and less heterogeneous in the study population. Because IE is a rare condition, our study population is too small to estimate specific prevalence's or risks, and therefore serves as a hypothesis-generating study. Since CCTA and ICA were not systematically performed in all patients and because different cut-offs were considered to determine significant stenosis, performance of these modalities could not be compared.

Conclusion

In our study population of patients with acute aortic valve IE the prevalence of CAD was approximately 12%. The risk of embolism after preoperative ICA seems low. CCTA can serve as a gatekeeper for ICA in most patients with acute aortic IE. More research is needed to analyze in which patients with CAD a concomitant CABG can safely be deferred.

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Table S1: Definition list

Inclusion criteria	
18 years of age or older at time of surgery	18 years of age or older at time of surgery
Valve repair or replacement for acute infective endocarditis	surgical (sternotomy or minimally invasive) surgery using repair/replacement techniques aimed at treating the infected valve(s)
Aortic valve affected	involvement of the aortic valve affected by episode of acute infective endocarditis
Active infective endocarditis	According to PA (derived during surgery) or ESC modified criteria for diagnosis of infective endocarditis 2015, only active when still on antibiotic treatment
Baseline	
Fulfilling modified Duke criteria?	Acute infective endocarditis according to the modified Duke criteria? (including PA-criteria)
Positive pathology/ histology of valve tissue	histology or tissue culture derived during surgery, positive for bacteria or active infection
Type of endocarditis (native, prosthetic)	nature of affected valve(s). If one of both is prosthetic, than prosthetic endocarditis. A homograft is scored as prosthetic valve endocarditis.
Presence of emboli prior to surgery	any evidence of embolic event to any organ (a.o. skin, brain, liver etc) prior to surgery
Stroke/TIA during active endocarditis prior to surgery	imaging and/or clinical evidence (by neurologist) of stroke/TIA, between onset and surgery
Micro-organism causing the endocarditis	According to 2015 ESC endocarditis guidelines for diagnostic criteria: typical micro organisms: at least 2 cultures, other micro organisms 2 or more >12h apart
Hypertension	presence of hypertension, as CAD2 -variable
Dyslipidemia	dyslipidemia, as CAD2 variable
Presence of vegetation on aortic valve	vegetation on aortic valve, diagnosed either by TTE, TEE, CT-scan
Size of vegetation on aortic valve	largest diameter in mm, in any direction
Presence of aortic valve regurgitation	as diagnosed by TTE, TEE, or MRI. If discordant, most severe measurement is collected
Presence of aortic valve stenosis	as diagnosed by TTE, TEE, or MRI. If discordant, most severe measurement is collected
Abscess	any intra cardiac abscess present
Mycotic aneurysm	any mycotic aneurysm present within the heart or ascending aorta
Presence of renal failure prior to surgery (at admission)	in three categories (eGFR) <30, 30-60, >60 ml/min/1.73 m2 using the CKD Epidemiology Collaboration (CKD-EPI) equation as per the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines
Left ventricular ejection fraction prior to surgery	as measured by TTE, TEE or MRI. If discordant, the most recent is chosen. Categories: poor (<30%), moderate (30-50%), normal >50%)

Table S1: Definition list *(continued)*

Presence of heart failure prior to surgery	initiation of diuretics, pulmonary oedema, need for hemodynamic support (mechanical, vasopressive or inotropic), cardiogenic shock
(a)typical angina	At time of presentation. According to the criteria of Diamond et al 1983, modified by the ACC/AHA in the 1999 guidelines for management of patients with chronic stable angina.
CAD2 clinical score	Following the risk score in stable angina patients by Genders et al; Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ. 2012;344:e3485. No angina was scored as non-specific (least severe). This score was not used as an absolute risk score, but rather to create insight into the different risk profiles between the diagnostic strategies.
Imaging data	
Status of coronary artery disease	known coronary status if cCTA or ICA was performed <12 months prior to surgery.
CT scan made for (a.o.) diagnosis of CAD	any CT scan acquired after diagnosis of endocarditis, with a protocol specifically allowing for evaluation of coronary arteries
CAG done for diagnosis of CAD	any CAG performed after diagnosis of endocarditis, that enables evaluation of coronary arteries
FFR of any coronary artery measured?	invasive FFR measurement of any coronary artery
Specification of measured FFR	ffr values of measured lesions
Presence of coronary artery disease	presence of any new anatomically significant (CAG HS >50%, rest >70%; CT >50%) lesion found during screening
Presence of significant coronary lesions during surgery	any anatomically significant (CAG HS >50%, rest >70%; CT >50%) lesion present during surgery, that has not yet been treated, including occluded prior bypass grafts, excluding prior succesfully bypassed native coronary lesions
Additional surgical data	
AoX time	Time from application of aortic clamp untill release
ECC time	Time from initiation of CPB to start of decannulation
Any bypass planned	as documented in medical files (planned, so already decided on before surgery)
Concomitant CABG	any bypass graft eventually performed during index surgery
Treatment of CAD during surgery	were all preoperatively diagnosed significant coronary lesions treated prior to or during surgery?
Outcome data	
Embolic event after preop CAG	any imaging or clinical evidence of arterial embolism <24h after start of CAG, or until start of index surgery, if it took place within 24h.

Table S1: Definition list *(continued)*

Renal failure after surgery	the lowest eGFR measured after surgery, in three categories (eGFR) <30, 30-60, >60 ml/min/1.73 m2 using the CKD Epidemiology Collaboration (CKD-EPI) equation as per the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines
Renal failure at time of discharge	the latest eGFR measured prior to discharge, in three categories (eGFR) <30, 30-60, >60 ml/min/1.73 m2 using the CKD Epidemiology Collaboration (CKD-EPI) equation as per the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines
Need for dialysis postoperatively	any need for CVVH or dialysis postoperatively during index admission
Perioperative myocardial infarction	according to third definition by thygesen et al (circulation 2012), but with CKMB (rather than cTnT, see Hueb et al 2016) >10x 99th percentile: 38 for women, 44 for men, together with either: (a) new pathological Q waves or new left bundle branch block, or (b) angiographic documented new graft or new native coronary artery occlusion, or (c) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Unplanned perioperative revascularization	any unplanned revascularization during index hospitalization, either by PCI or surgery

Table S2: Type of surgery per group

	All patients (n=159)	No diagnostics (n=46)	CAD status known (n=14)	Initially CT-group (n=54)	Initially ICA-group (n=45)
Aortic valve replacement	100% (159)	100% (46)	100% (14)	100% (54)	100% (45)
Concomitant mitral valve surgery	24% (38)	20% (9)	21% (3)	28% (15)	24% (11)
Concomitant aortic root surgery	36% (57)	50% (7)	59% (27)	26% (14)	20% (9)
Concomitant CABG (planned)	3% (5)	0	0	0	11% (5)
Concomitant CABG (performed)	6% (9)	4% (2)	7% (1)	0	13% (6)
Surgery for prosthetic valve endocarditis	37% (59)	50% (23)	71% (10)	32% (17)	20% (9)

Table S3: Renal function in all patients.

Renal failure			
All patients (n=159)	Discharge:	>60 eGFR	70% (111)
		30-60 eGFR	20% (32)
		<30 eGFR	5% (8)
		Unknown	5% (8)
	Decrease lowest postop:	0 or higher	67% (106)
		-1	25% (39)
		-2	7% (11)
		Unknown	2% (3)
	Decrease at discharge:	0 or higher	87% (139)
		-1	6% (9)
		-2	2% (3)
		Unknown	5% (8)
	Need for dialysis		8% (13)
	New need for dialysis		6% (10)

Renal function in patients with approach of cCTA first or ICA directly.

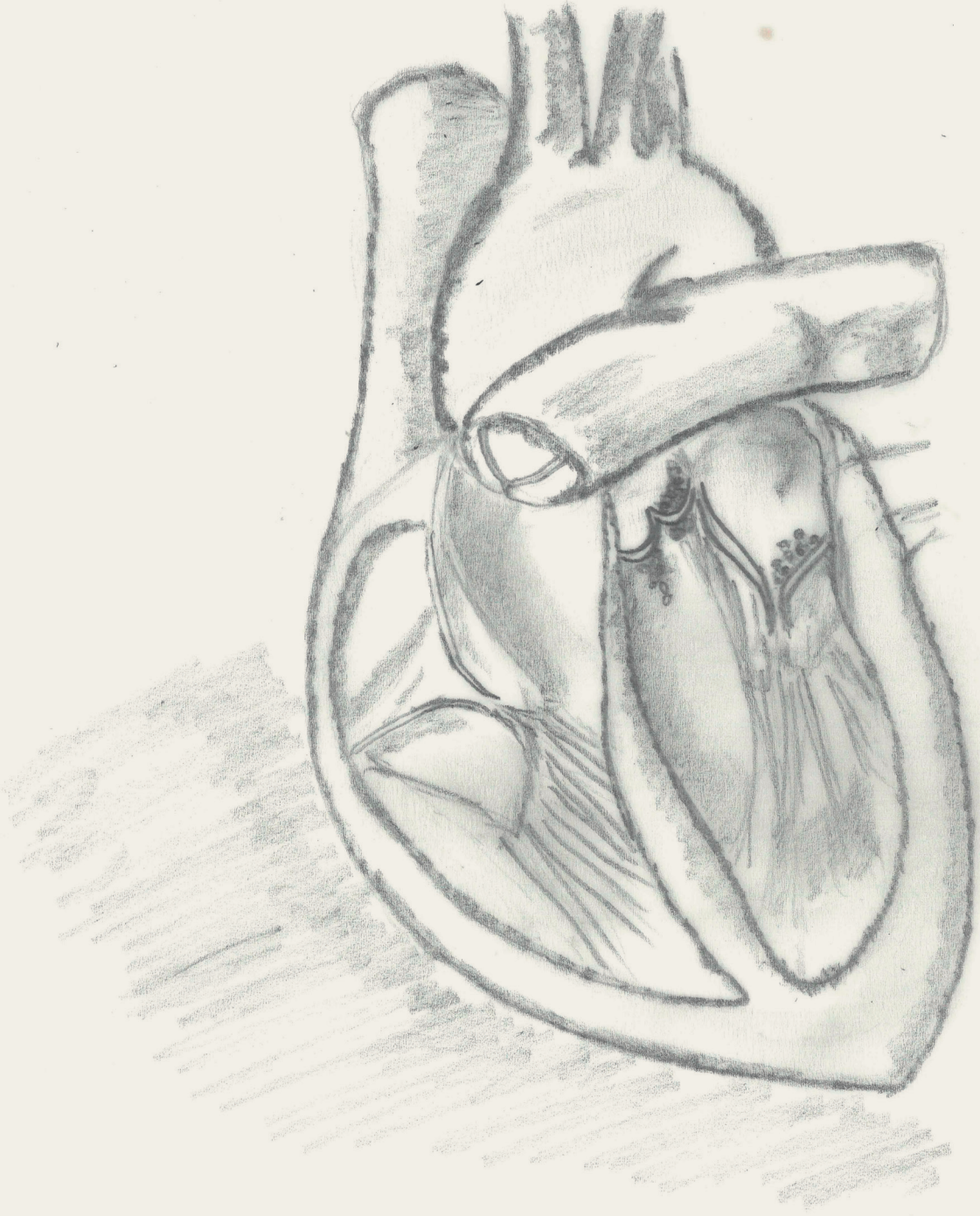
Renal failure (cCTA first vs ICA directly)				
		cCTA (n=54)	**ICA(n=45)**	**p-value***
Renal function at time of presentation	eGFR >60	61% (33)	53% (24)	0.16
	eGFR 30-60	35% (19)	31% (14)	
	eGFR <30	4% (2)	16% (7)	
	Dialysis	0	7% (3)	0.09
Renal function lowest after surgery	eGFR >60	44% (24)	24% (11)	0.07
	eGFR 30-60	35% (19)	36% (16)	
	eGFR <30	20% (11)	38% (17)	
	New dialysis	6% (3)	18% (6)	0.21
Renal function at discharge	eGFR >60	76% (41)	60,0% (27)	0.35
	eGFR 30-60	19% (10)	27% (12)	
	eGFR <30	4% (2)	7% (3)	
Decrease lowest after surgery:	0 or higher	69% (37)	49% (22)	0.12
	-1	22% (12)	41% (18)	
	-2	9% (5)	7% (3)	
Decrease at discharge:	0 or higher	89% (48)	87% (39)	0.75
	-1	6% (3)	7% (3)	
	-2	4% (2)	0	

* renal function was compared at each time point separately.

Epilogue

"Always consider your intellect to be lacking; otherwise too much faith in it surely leads to error."

Imam Ali (A)



Chapter 10

Summary

Summary in Dutch | Nederlandse samenvatting

General discussion

List of publications

PhD-portfolio

About the author | Curriculum Vitae

Acknowledgement | Dankwoord

Summary

Introduction

Infective Endocarditis (IE) is a destructive and overwhelming cardiovascular disease with high mortality, which can be difficult to diagnose and manage. In 2015, the European Society of Cardiology (ESC) introduced new guidelines for IE to help facilitate the management of this challenging disease. The guidelines encouraged the consultation of a multidisciplinary team (The Endocarditis Team) in all cases of (suspected) IE and updated the diagnostic work of patients with suspected IE by including new imaging modalities: the use of ^{18}F-FDG PET/CT for the detection of metabolic active periprosthetic heart valves as well as extracardiac infectious foci. Furthermore, the use of cardiac CTA is advised for a detailed anatomical depiction of the heart in all phases of the cardiac cycle. However, literature about the image acquisition, interpretation as well as the applicability of these two imaging techniques was still relatively limited at the time the guideline was written.

The aim of the present thesis was to investigate the implementation of the 2015 ESC guidelines for IE in The Netherlands (part I), and to investigate the value of a multidisciplinary approach in the management of IE and to provide possible alternative ways to sustain this approach safely, especially during the COVID-19 pandemic (part II). This thesis also provides normal PET/CT reference imaging findings and values after prosthetic valve (and ascending aortic prosthesis) implantation and explores the additional diagnostic value of PET/CT and cardiac CTA in the diagnosis of infective endocarditis in specific patient populations (part III). In addition, it evaluates the current role of cardiac CTA in patients with IE, especially in the detection of coronary artery disease (part IV).

Part I

In part I of this thesis we addressed the implementation of the latest ESC guidelines for IE in the Netherlands (**chapter 2**). With the help of a working group created by the Dutch Society of Cardiology, a country wide survey was conducted to investigate current Dutch IE practices. Based on the results of this survey it was concluded that the ESC guidelines need some adjustments for implementation in The Netherlands. These adjustments varied from a less restrictive pre-operative screening and treatment of nasal carriers of Staphylococcus aureus to the recommendation of adjusted antibiotic use for treatment of IE according to the Stichting Werkgroep Antibioticabeleid (SWAB; Dutch Working Party on Antibiotic Policy) guidelines instead of antibiotic regimens proposed by the ESC guidelines.

Part II

In part II, we tried to investigate the impact of the multidisciplinary approach, with the suggested use of the Endocarditis Team by the ESC guidelines. In **Chapter 3** we provided data of 4 years of experience with the Endocarditis Team from a prospective registry. We

hypothesized that the Endocarditis Team would have clear impact on the diagnostic work up and therapy of patients with suspected IE. Based on the results and provided data in this study, the Endocarditis Team recommendations resulted in a 17% change in diagnosis, a 42% change in antibiotic treatment and 5% change from conservative to invasive treatment which implies that a multidisciplinary approach results in a difference in patient management recommendations in about half of the patients.

In **Chapter 4** we addressed the challenges of the adaptation to the new rules in the times of COVID-19 pandemic and continuation of the multidisciplinary approach for IE. In this chapter we proposed solutions to adhere to the new gathering restriction rules and at the same time maintain the multidisciplinary approach for the management of cardiac diseases. The proposed solutions consisted of an "adjusted physical method" which implied a physical attendance of the meeting but with additional social distancing rules, "video conferencing", "electronic communication" through e-mails and/or the use of electronic patient files and "virtual reality and extended reality (VR and XR)", which is a new and growing way of communication in different fields of medicine. All of these methods had their significant drawbacks: for the adjusted physical method this was the remaining small risk of spreading the virus, for the video conferencing method this was the problems that come along with internet connection issues as well as loss of visual expression and body language due to the often-limited visuals during a video call, for electronic communication the drawback was the major time consumption of the meeting and for the VR/XR method this was the unavailability of the necessary hardware and software. However, all these drawbacks and challenges can be solved to minimize the risk of spread of COVID-19 and still be able to provide good patient care. Finally in **Chapter 5** a new way of communication for physicians in multidisciplinary setting through VR was tested. We hypothesized that VR would be easy to use and have advantages over other digital communication methods in a multidisciplinary setting. The results confirmed this with mentioned advantages such as "User-friendliness", "safety", "multidisciplinary and multi-user engagement in the conversation", and "possibility to evaluate clinical imaging data" by the participants of the study. The dependency on IT-infrastructure, the poor quality of the images, and the need to wear uncomfortable VR-hardware were some of the disadvantages of using VR for multidisciplinary meetings. To improve the feasibility of VR for multidisciplinary meetings in the future, the use of a highly secure platform which is connected to the electronic health record is preferred.

Part III

Normal PET/CT findings after uncomplicated aortic valve and ascending aortic prosthesis implantation are needed for correct identification and interpretation of pathological 18F-FDG uptake and were provided in part III. Moreover, the usefulness of PET/CT and cardiac CTA was tested in specific patient populations with suspected IE. In **Chapter 6** we provided normal perivalvular 18F-FDG uptake on PET/CT in the first year after an uncomplicated

aortic prosthetic heart valve (PHV) implantation. After the visual and quantitative analyses of perivalvular 18F-FDG uptake in 37 PET/CT scans derived from 37 patients scanned either 5 weeks, 12 weeks or 1 year after the PHV implantation, we concluded that the 18F-FDG uptake pattern, visual and quantitative analyses were similar in all patients with mostly a circular pattern and low to intermediate 18F-FDG uptake.

In **Chapter 7**, we provided normal 18F-FDG uptake patterns and intensity around aortic root and/or ascending aorta prosthesis (ARAP) at three different locations of the prosthesis. A total of 20 individuals with an ARAP (e.g., Bentall-procedure or supra coronary ascendens replacement (SCAR)), underwent 18F-FDG PET/CT at either at 3 months or 1 year after implantation. After visual and quantitative analyses of the images on three different locations of the prosthesis ("cranial anastomosis (CA)", "prosthetic heart valve (PHV)", "ascending aorta prosthesis (AAP)"), it was concluded that the 18F-FDG uptake patterns were homogeneous diffuse with low to intermediate intensity on different areas of the prosthesis and that there were no significant differences between 18F-FDG uptake at 3 months and 1 year after ARAP implantation. However, due to the possibility of 18F-FDG uptake on multiple areas of the prosthesis with multiple uptake patterns and intensities, it was also concluded that the interpretation of 18F-FDG PET/CT in the first year after ARAP implantation should be done very carefully to avoid mistakes.

In **Chapter 8** we evaluated the additional diagnostic value of 18F-FDG PET/CT and cardiac CT in patients with suspected infective endocarditis of a transcatheter implanted aortic valve (TAV-IE). A total of 30 patients from 6 different hospitals who had undergone 18F-FDG PET/CT and cardiac CT for suspected TAV-IE were retrospectively included. After adding the 18F-FDG PET/CT and cardiac CT to the conventional Duke criteria and letting the Endocarditis Team provide the final diagnosis through modified ESC criteria, it was concluded that the addition of these 2 imaging tools can change the diagnosis in 33% of the patients.

Part IV

In this part of the thesis, we explore the value of cardiac CT in the diagnostic and therapeutic management of patients with IE of the aortic valve for assessing the coronary arteries. The coronary status of patients with IE, who are in risk of coronary artery disease (CAD), needs to be clarified before any valve surgery in order to determine whether concomitant coronary artery bypass graft (CABG) is needed. However, in patients with IE of the aortic valve, the necessity of screening for CAD and the risk of embolization due to invasive coronary angiography (ICA) is debated. In **Chapter 9** we evaluated the safety and feasibility of ICA and cardiac CT to diagnose CAD. After careful evaluation of 159 retrospective included patients from a single center, we concluded that although the risk of embolization after ICA is low, cardiac CT still can serve as a gatekeeper for ICA in most patients with IE of the aortic valve.

Summary in Dutch | Nederlandse Samenvatting

Introductie

Infectieuze endocarditis (IE) is een destructief en zeer ernstig cardiovasculair ziektebeeld dat moeilijk te diagnosticeren en te behandelen is en gepaard gaat met een hoge mortaliteit. De Europese vereniging van cardiologie (ESC), heeft in 2015 nieuwe richtlijnen geïntroduceerd voor de behandeling van dit uitdagende ziektebeeld. Deze richtlijnen adviseren om een multidisciplinair team (het Endocarditis Team) te consulteren in alle gevallen van een (verdenking op) IE. Verder geven de richtlijnen een update met betrekking tot het diagnostisch beleid door het invoeren van nieuwe beeldvormende technieken: het gebruik van ^{18}F-FDG PET/CT voor de detectie van metabole activiteit in het lichaam die kan wijzen op infectiehaarden en het gebruik van cardiale CT voor een gedetailleerde weergave van de cardiale anatomie in alle fasen van de hartcyclus. Echter, ten tijde van de introductie van de richtlijnen was nog weinig bekend in de literatuur over de toepasbaarheid van deze beeldvormende technieken en de interpretatie van de verkregen beelden bij patiënten met IE.

Het doel van dit proefschrift is om de implementatie van de ESC richtlijnen voor IE uit 2015 in Nederland te onderzoeken (**deel I**), en om de waarde van een multidisciplinaire benadering met betrekking tot het beleid bij IE, met name in de tijd van de COVID-19 pandemie, te onderzoeken (**deel II**). Dit proefschrift beschrijft tevens het spectrum van de normale ^{18}F-FDG PET/CT bevindingen en waarden na een implantatie van een kunsthartklep en/of aorta prothese > Daarnaast is ook de aanvullende diagnostische waarde van ^{18}F-FDG PET/CT en cardiale CT bij specifieke patiënten populatie met verdenking op IE onderzocht (**deel III**). Daarnaast evalueert dit proefschrift de huidige rol van cardiale CT in patiënten met IE, voornamelijk voor de detectie van coronair lijden (**deel IV**).

Deel I

In deel I van dit proefschrift richten we ons op de implementatie van de meest recente Europese richtlijnen over IE in Nederland (**Hoofdstuk 2**). Met de hulp van een werkgroep opgezet door de Nederlandse Vereniging voor Cardiologie (NVVC) werd er een nationale enquête uitgezet om het huidige Nederlandse beleid met betrekking tot IE te onderzoeken. Op basis van de resultaten van deze enquête is geconcludeerd dat de Europese richtlijnen op enige punten aangepast moest worden voordat ze in Nederland konden worden geïmplementeerd. Deze aanpassingen varieerden van een milder beleid voor de screening en behandeling van Staphylococcus aureus bacterie dragerschap tot aan een aangepast antibiotisch beleid voor de behandeling van IE volgens de richtlijnen van Stichting Werkgroep Antibioticabeleid (SWAB) in plaats van de voorgestelde antibiotische behandeling in de Europese richtlijnen.

Deel II

In deel II, hebben we de waarde van de multidisciplinaire benadering voor patiënten met IE onderzocht. In **Hoofdstuk 3** is data van onze ervaring met het Endocarditis Team gedurende 4 jaar weergegeven. Onze hypothese was dat het Endocarditis Team een duidelijke invloed zou hebben op het diagnostisch en therapeutisch beleid bij patiënten met verdenking op IE. De resultaten van dit onderzoek toonden aan dat door het beleidsvoorstel van het Endocarditis Team er in 17% van de patiënten een verandering van diagnose optrad, in 42% een verandering in het antibiotisch beleid en in 5% een verandering van conservatieve naar chirurgische behandeling. Dit geeft aan dat een multidisciplinaire benadering zorgt voor een aangepast medisch beleid in ongeveer de helft van patiënten met IE.

In **Hoofdstuk 4** hebben we aandacht besteed aan de uitdagingen die ontstaan zijn door de nieuwe regels omtrent de COVID-19 pandemie. In dit hoofdstuk hebben we oplossingen voorgesteld om de multidisciplinaire benadering voor cardiale ziektebeelden voort te kunnen zetten waarbij tegelijkertijd aan de nieuwe regels voor bijeenkomsten tijdens COVID-19 pandemie wordt voldaan . De voorgestelde oplossingen bestonden uit een “aangepaste fysieke methode”, waarbij participanten met aangepaste afstand regels fysiek aanwezig zijn, “video conferentie”, “elektronische communicatie” waarbij communicatie alleen plaats vindt door e-mails of het gebruik van elektronische patiëntendossiers en als laatste het gebruik van “virtual/extended reality (VR/XR)” wat een nieuwe communicatiemethode in de medische wereld is. Alle genoemde methoden hadden hun nadelen. Voor de aangepaste fysieke methode is het nadeel dat ondanks het hanteren van afstand regels er nog steeds een kleine kans bestaat op het verspreiden van het virus. Communicatie via videoconferentie gaat vaak gepaard met internetconnectie problemen, maar ook een vermindering in het waarnemen van gezichtsuitdrukkingen en non-verbale communicatie doordat het beeld hiervoor tijdens videobellen niet optimaal genoeg is. Voor elektronische communicatie is het nadeel voornamelijk de benodigde tijd en voor communicatie via VR/XR is het grote nadeel de afwezigheid van de benodigde apparatuur en software. Echter, al deze nadelen kunnen worden opgelost zodat het risico op verspreiding van COVID-19 geminimaliseerd wordt.

Als laatste, is in **Hoofdstuk 5** geëxperimenteerd met VR als communicatiemethode voor de opzet van een multidisciplinaire bijeenkomst. Onze hypothese was dat VR makkelijk te gebruiken zou zijn en voordelen zou hebben ten opzichte van andere digitale communicatie methoden in een multidisciplinaire setting. De resultaten bevestigden dit met voordelen als “gebruiksgemak”, “veiligheid”, “multidisciplinair en meer persoonsgebonden communicatie” en “mogelijkheid om klinische beelden te evalueren”. “De afhankelijkheid van techniek”, “de lage kwaliteit van klinische beelden” en “het oncomfortabele VR hardware” waren een paar van de genoemde nadelen voor het gebruik van VR. Om de toepasbaarheid van VR te verbeteren voor het gebruik tijdens multidisciplinaire bijeenkomsten, dient er in de

toekomst gebruik te worden gemaakt van een goed beveiligd platform dat verbonden is met het elektronische patiënten dossier.

Deel III

Referentie waarden van normale PET/CT bevindingen na een ongecompliceerde kunsthartklep en/of aortaprothese implantatie zijn nodig voor een correcte interpretatie van 18F-FDG PET/CT beelden die worden gebruikt voor de diagnostiek van endocarditis. Verder, is de bruikbaarheid van de PET/CT en cardiale CT vooralsnog zeer beperkt getest in specifieke patiëntenpopulatie met verdenking op IE. In **Hoofdstuk 6** hebben we bij patiënten met een ongecompliceerde aortaklepimplantatie, de normale 18F-FDG opname in het eerste jaar na implantatie onderzocht. Bij 37 patiënten die op 5, 12 of 52 weken na implantatie een PET/CT ondergingen werd een visuele en een kwantitatieve analyse van de opname rondom de kunstklep verricht . Hieruit werd geconcludeerd dat zowel het opname patroon, als de visuele en kwantitatieve beoordelingen gelijk waren in alle patiënten met bijna overal een laag tot gemiddeld 18F-FDG opname met een circulair patroon.

In **Hoofdstuk 7** hebben we het normale 18F-FDG opname patroon en de opname intensiteit rond een aortawortel en/of aorta-ascendens prothese (ARAP) op drie verschillende punten van de prothese onderzocht. In totaal ondergingen 20 patiënten met een ARAP een PET/CT op 3 maanden of 1 jaar de implantatie. Na visuele en kwantitatieve beoordeling van drie delen van de prothese (craniale anastomose, kunstklepniveau en de aorta-ascendens prothese), concludeerden we dat 18F-FDG opname patroon en de intensiteit vergelijkbaar waren op 3 maanden en 1 jaar na implantatie met een homogeen diffuse opnamepatroon en lage tot gemiddelde intensiteit.

In **Hoofdstuk 8** hebben we de aanvullende diagnostische waarde van 18F-FDG PET/CT en cardiale CT in patiënten met verdenking op een geïnfecteerde percutane aortaklep (transcatheter aortic valve implantation: TAVI) geëvalueerd. In totaal werden 30 patiënten vanuit 6 verschillende ziekenhuizen geïncludeerd die een 18F-FDG PET/CT en een cardiale CT hadden ondergaan voor verdenking op infectie van de TAVI. Na het toevoegen van 18F-FDG PET/CT en de cardiale CT aan de diagnostische Duke criteria werd de diagnose opnieuw gesteld door het Endocarditis Team. Hierbij werd geconcludeerd dat het toevoegen van deze 2 beeldvormende technieken de diagnose in 33% van de patiënten kan veranderen.

Deel IV

In dit deel van het proefschrift hebben we de diagnostische en therapeutische waarde van de cardiale CT voor het vaststellen van coronair lijden bij patiënten met IE van de aortaklep geëvalueerd. De aan- of afwezigheid van vernauwingen in de kransslagaders bij patiënten met IE, die een risico hebben op coronair lijden, dient vastgesteld te worden voor een klepoperatie plaats heeft, zodat een eventuele “coronary artery bypass graft”(CABG)

tegelijk uitgevoerd kan worden. Het vaststellen van de status van kransslagaders wordt normaal door een diagnostische hartkatheterisatie uitgevoerd. Echter is de noodzaak voor het uitsluiten van coronair lijden met het risico op embolisatie van de vegetatie op de aortaklep door een diagnostische hartkatheterisatie dubieus. In **Hoofdstuk 9** hebben we de veiligheid en toepasbaarheid van diagnostische hartkatheterisatie en cardiale CT voor de diagnostiek van coronair lijden geëvalueerd. Na evaluatie van 159 geïncludeerde patiënten uit één ziekenhuis, concludeerden we dat alhoewel het risico op embolisatie na diagnostische hartkatheterisatie laag is, cardiale CT wel als een “poortwachter” kan dienen voor de diagnostische hartkatheterisatie in meeste patiënten met IE van de aortaklep.

General discussion

Infective endocarditis has always been a disease that is difficult to diagnose and treat. The current guidelines and the availability of new imaging techniques have given an important new impulse to tackling these problems but have not completely solved them. Moreover, new developments also lead to new challenges. For instance, the implementation of European or American guidelines can be challenging in individual countries, since not all recommendations are feasible everywhere due to local laws, reimbursement issues, regulations and more importantly because the necessities for implementing the recommendations simply are not available or immediately feasible. Furthermore, the interpretation of the proposed new imaging techniques needs to be enhanced and the collaboration between different disciplines needs to be improved to manage this intricate disease.

Implementation of the guidelines

Medical guidelines, as it is implied by the name, are usually introduced to guide one in making the right decisions for the management of a specific disease. Continental guidelines are usually composed by incorporating the results of multiple large trials, smaller studies, and the opinions of physicians from different countries who are experts in the field. The recommendations of guidelines are therefore almost always a compromise by consensus. However, it cannot be assumed that the implementation of all recommendations in the guidelines is possible in every country, since differences in regulations and the presence/absence of technological requirements and logistical challenges can impede this process. In general, after the introduction of continental guidelines, experts of every country should make nationwide versions of the guidelines that are based on the continental guidelines but are adjusted to the specific situation in their country. The ESC guidelines for IE were evaluated by the Dutch federation of medical specialists (FMS) for implementation in the Netherlands and were endorsed by the Dutch society for Cardiology (NVVC) with some minor adjustments. These adjustments consisted of less restrictive pre-operative screening and treatment of nasal Staphylococcus aureus carriers, proposition of the Endocarditis Team to be a quality indicator in tertiary centers, the use of SWAB guidelines for the antibiotic treatment and a simplified demonstration of imaging and microbiological diagnostic techniques with flowcharts that were discussed in detail in Chapter 2.

Part of the evaluation of the guideline implementation in the Netherlands was a nationwide survey that demonstrated that the ESC recommendations were mostly followed by the cardiologists in the Netherlands. For example, the Endocarditis Team was already consulted in various cardiothoracic centers for all patients with suspected IE. Furthermore PET/CT and CTA were widely used in the diagnostic workup of patients with IE. However, slight adjustments of some of the ESC recommendations were suggested such as "the pre-operative screening and/or treatment of nasal carriage of Staphylococcus aureus" and "the

timing of surgery" which is suggested to be determined by the specialists involved. The adjustment of the ESC guidelines to the local situation in the Netherlands a relatively long time. Ideally however, such adjustments to the worldwide or continental guidelines are made shortly after the introduction, in order to help clinicians make the right evidence-based decisions as soon as possible.

Multidisciplinary meeting

Multidisciplinary meetings are extremely important for providing good care, especially for patients with (multiple) complex diseases like IE. For this reason, the European Society of Cardiology (ESC) recommends in its latest guidelines for IE to discuss all patients with (suspected) IE in a multidisciplinary Endocarditis Team (1). The guidelines were supported by the results of a few studies showing a decrease in mortality after the introduction of a multidisciplinary approach (2, 3). However, there are challenges in setting up a multidisciplinary Endocarditis Team, such as formation of the team with right specialists, logistical problems such as planning the right time and location for the meeting and preparation/introduction of the cases as well as communication and execution of the outcome of the meetings to the referring physicians. Part of these challenges could be met by having a dedicated coordinator who keeps an overview of the cases that need to be discussed and who plays a key role in the preparation and presentation of the cases, the management of the endocarditis team and finally in returning the advice to the referring physician. In Chapter 3 we described our experience in setting up a multidisciplinary Endocarditis Team in our tertiary medical center and the results of the first 321 patients who were discussed in the meetings. It was notable that microbiological and imaging tests were performed more often as a result of the Endocarditis Team meetings. Interestingly, this also led to a relatively high rate of change in diagnosis (7%) and change from conservative to surgical treatment in 5% of the cases. The mortality rate of the discussed patients with a median follow up of 23 months was 28%. From the know literature, the mortality rate of patients with IE is 17% in the first 2 months and 27% in the first 6 months after diagnosis. The recommendations of the Endocarditis Team may also have an effect on the outcome of patients' mortality.

Since imaging tests such as cardiac Computed Tomography (CT) and 18F-FDG PET/CT were advised more often in the diagnostic workup according to the guidelines (1), the presence of a cardiac radiologist or cardiac imaging specialist during an Endocarditis Team discussion is necessary. The results of the study stress the severity of this life-threatening disease and the necessity for the implementation of a multidisciplinary approach for its management.

COVID-19 and innovation

Because of gathering restriction rules during the COVID-19 pandemic another challenge in setting up the multidisciplinary meetings had suddenly emerged. Although it was necessary

to discuss patients in multidisciplinary meetings in order to provide good patient care, the rules restricted live presence of multiple specialists in one place. However, there are multiple innovative ideas to enable and facilitate the continuation of multidisciplinary meetings in the times of the COVID-19 pandemic in a safe way. In Chapter 4 we described examples of these innovative ideas as well as their advantages and disadvantages. It is important to realize what the possibilities are for different communication methods in line with the gathering restriction rules, to set up multidisciplinary meetings in a safe way.

One of these alternative communication methods is the use of Virtual Reality (VR), which is an innovation that is growing in popularity in the field of medicine (4, 5). In Chapter 5 we presented a proof of concept in which we provided the feasibility and the added value of VR for multidisciplinary meetings. Most of the participants indicated the convenient and easily operated way of VR and confirm the feasibility of VR for multidisciplinary meetings in the future, especially under the gathering restriction rules. Although there are shortcomings in the use of VR for teleconferencing, such as availability of the hardware and software, poor image quality and connecting issues, the potential of VR to be an indispensable feature in the medical field in the future is undeniable. Ideas such as enabling real-time clinical assessment of patients that are hospitalized in other medical centers or who are in quarantine can become reality in the near future.

New imaging techniques

Diagnosis of IE is usually made using the modified Duke criteria which contains positive signs for IE on transthoracic or trans-esophageal echocardiography (TTE/TEE) as a major criterium (6). In their latest guidelines for management of IE the ESC introduced a new set of criteria (1) based on the modified Duke criteria with the addition of use of extra diagnostic imaging techniques such as cardiac CT and 18F-FDG PET/CT for certain patient population. However, one can say that the recommendation of 18F-FDG PET/CT in these guidelines was somewhat early (or even premature), since the available literature at that time was limited and how to distinguish pathological from physiological 18F-FDG uptake after recent valve/aortic prosthesis implantation was not yet clear. Misinterpretation of 18F-FDG PET/CT in patients with a suspected infected prosthetic valve and/or aorta can have severe therapeutic and prognostic consequences. Patients may be treated while this is not necessary or not be treated while this is obligatory. Furthermore, the guidelines advised to adhere to a 3 months safety period after valve implantation before performing 18F-FDG PET/CT for the diagnosis of IE, in order to avoid possible false positive 18F-FDG uptake around the new implanted valve. However, this recommendation was not based on any literature.

In Chapter 6 we provided insight in the normal periprosthetic 18F-FDG uptake patterns and severity after aortic valve implantation based on visual and quantitative analyses which may help clinicians in distinguishing pathological from physiological 18F-FDG uptake. Interestingly,

the 18F-FDG uptake around the prosthetic valve appeared to be of low intensity shortly (5 weeks) after implantation and in addition this was not significantly different from the uptake 1 year after the implantation. According to this, the advice of the ESC not to perform 18F-FDG PET/CT for detection of IE in the first 3 months after valve implantation to prevent false positive results needs to be reconsidered. Corroborating with the results of other studies we provided circular (homogeneous diffuse) uptake patterns with low intensity to be more likely physiological. A cut off value for the quantitative analyses of 18F-FDG with the ratio of standardized uptake values and the background intensity (SUVratio) can be found in the literature (7). However, the results of our study suggested that this value may be slightly higher than the previous reported value of 2.0.

The normal 18F-FDG uptake around ascending aorta prostheses after recent implantation, was assessed in Chapter 7. According to the results of this study, there were no significant differences between 18F-FDG uptake shortly (3months) and 1 year after prosthesis implantation. However, since there are multiple locations to analyze the FDG uptake on the aortic prosthesis, and the intermediate-high FDG uptake intensity that was seen in about 50% of the patients in our study, it could be challenging to determine the uptake pattern, which could lead to mistakes in the interpretation of the images. Therefore, the use of 18F-FDG PET-CT in the first year after ascending aorta prosthesis implantation for the detection of infection of such prostheses needs to be done carefully taking the normal variability into account to avoid mistakes. One of the potential ways to differentiate between physiological and pathological 18F-FDG uptake, is to treat patients with antibiotics if there is suspicion of pathological uptake and to repeat the PET/CT after 6 weeks. If the 18F-FDG uptake has not changed under antibiotic treatment, the uptake is probably false positive and in case of reduction of uptake intensity and pattern , the uptake is most certainly true positive. However, this way of differentiation is based on common sense and needs to be confirmed by studies and/or clinical trials.

Other ways of differentiating between false positive or true positive uptake, is by using an additional radiolabeled leucocyte scintigraphy scan (LS). By comparing an area with 18F-FDG uptake on the PET/CT with the exact area on the LS, one can distinguish whether the uptake is caused by infective of inflammatory response. However, it should be mentioned that the contrast to noise ratio of the radiolabeled LS images is usually poor and that this imaging technique has a possible lower diagnostic sensitivity for IE on its own(8, 9).

Another specific patient population that needs differentiation in the analysis of 18F-FDG PET/CT for the detection of IE, are patients with transcatheter aortic valve implantation (TAVI). According to the ESC guidelines 18F-FDG PET/CT can be used for the diagnosis of prosthetic valve IE and this should apply to detection of IE of the TAVI (TAV-IE) as well. However, since transcatheter valves are of a different design and material than surgically implanted valves

and, importantly, are implanted in a fundamentally different way, this could potentially affect the 18F-FDG uptake pattern and intensity. In Chapter 8 we provided the additional value of 18F-FDG PET/CT and cardiac CT for the diagnosis of TAV-IE. In addition to the modified Duke criteria, it appears that 18F-FDG PET/CT and cardiac CT with the support of a multidisciplinary Endocarditis Team can help further differentiate patients with suspected TAV-IE in either rejected IE or definite IE. These diagnostic alterations as a result of adding PET/CT and CTA in the diagnostic criteria for suspected TAV-IE may affect the morbidity and mortality, by changing the therapeutic policy of patients with “possible TAV-IE”. Since most of the time surgical valve replacement is not preferred or not possible in patients with TAV-IE, this change of therapeutic policy can mainly happen in antibiotic treatment. In patients with persistent 18F-FDG uptake after regular antibiotic treatment period, who are at high risk of relapse, prolongation of antibiotic duration or even starting lifelong antibiotic suppression therapy may be in order. Furthermore, the effect of the antibiotic treatment can possibly be tested with a series of 18F-FDG PET/CT scans to evaluate the downtrend of 18F-FDG uptake and if needed adjustment of antibiotic dosage or type can be implemented. However, the detection of pathological 18F-FDG uptake without available baseline patterns and values of intensity for transcatheter valves are somewhat of a speculation. Further research in this matter to provide normal uptake after TAVI is needed.

Cardiac CT is nowadays used often in diagnostic work-up of patients with (suspected) IE. The role of cardiac CT is complementary to echocardiography and does not replace this imaging tool for the diagnosis of IE. Transesophageal echocardiography has a great temporal resolution and is especially indispensable in the detection of very mobile vegetations that can be missed by cardiac CT. Furthermore, echocardiography is essential in the determination of the severity of valve leakage/stenosis. However, cardiac CT is of great value in patients with contraindication for undergoing transesophageal echocardiography or patients with prosthetic valves of which assessing good quality imaging with echocardiography can be challenging. Furthermore, during the time of the COVID-19 pandemic, it may be favorable to avoid transesophageal echocardiography if there is a less "invasive" alternative. Especially in patients with peri annular extensions, the size and the severity of the abnormality can be demonstrated in detail. The role of cardiac CT is not limited to providing good quality imaging of the suspected valve, since this imaging technique can also be used for the assessment of pre-operative coronary status in patients undergoing valve surgery due to IE (13). In theory the of use invasive coronary angiography (ICA) in patients with IE of the aortic valve can be risky since there is a chance of embolization of a mobile vegetation on the aortic valve due to contact with the catheter. Both the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines on IE make an exception for patients with IE of the aortic valve to undergo invasive coronary angiography if the chance of embolization is too high(1, 14). However, this is not further specified. In CH 10 we described the outcome of patients with aortic valve IE undergoing preoperative

screening of the coronary status by either cardiac CT or ICA. We found that cardiac CT can serve as a gatekeeper for ICA in patients with acute presentation of IE of the aortic valve. Furthermore, only 1 patient out of 52 who suffered from embolization after undergoing ICA, and although the risk of embolization seems low it most likely depends on the location, size and mobility of the vegetation and the physician awareness of the vegetation. In cases where the presence of an aortic vegetation is known, a more careful approach can be used with regard to wire handling and contrast injection.

Future perspectives

Further improvements in the imaging techniques

The introduction of 18F-FDG PET/CT for the diagnosis of IE in the 2015 ESC guidelines, seemed scientifically somewhat early and it turned out to be visionary. However, there were some unknown factors such as the baseline 18F-FDG uptake patterns and quantitative values. Nuclear imaging has proven to be a reliable additional diagnostic technique in endocarditis patients provided that pitfalls and imaging optimalization are taken into account.

One of the factors, which is still unknown to this day, is the optimal imaging time after 18F-FDG injection for detection of infection/inflammation. The current PET/CT imaging protocol is based on oncology and the detection of active (tumor) cells, and starts about 60 minutes after 18F-FDG injection. However, cells involved in infection/inflammation could take up 18F-FDG much faster/slower than 60 minutes. In order to understand the 18F-FDG kinetics in infection/inflammation and to provide an optimal imaging time after 18F-FDG injection, dynamic PET/CT imaging studies that acquire imaging data from the start of 18F-FDG injection to several hours after injection are needed.

Furthermore, both respiratory and cardiac motion can cause blurry PET/CT images. A possible solution to prevent this, is respiratory and ECG gated PET/CT imaging which uses images only from the prespecified parts of the respiratory and cardiac cycles.

Another technique to improve the sensitivity of the images, is the use the new whole-body PET/CT scanners. Current PET/CT scanners have an approximately 20cm axial field of view, which means that during the scan about 80-90% of the patients' body is outside this field of view and no signals from this part is being collected. The new whole-body PET/CT scanners have a 5-10 times larger field of view which enables a large portion of the body to be scanned at once. This can improve the effective sensitivity, while the scan takes a shorter amount of time and less radiation is needed. Although the current PET/CT scans have a large enough field of view for the detection of infected/inflamed tissue around the heart valves, the detection of septic emboli that can be present anywhere in the body is more challenging.

The new whole-body PET/CT scans can be of great value in this matter, however, further research with these new scanners is needed in order to confirm these benefits.

A more futuristic idea to improve PET/CT imaging is the use of new tracers. Currently 18F-FDG is the most common tracer used for detection of infection/inflammation and also in the field of oncology to detect tumor cells that use a large amount of glucose. However, theoretically, new tracers that are based on specific proteins on the cellular membrane of bacteria may help in the detection of these bacteria inside the body.

Prevention of embolization is one of the criteria for performing urgent surgery in patients with IE. However, the risk in embolization is established by confirming a recent embolization under adequate antibiotic treatment, which is contradicting the "prevention of embolization". In addition, cerebral (micro)embolization due to IE, can be present in asymptomatic patients, especially in the early stages of the disease. An MRI can detect recent cerebral embolization, however new embolization under antibiotic therapy cannot be distinguished with recent embolization before the use of antibiotic therapy. Therefore, by performing an MRI in the early stages of confirming the diagnosis of IE, the radiologist can have baseline images, which can be used as control material if a new MRI is necessary.

Furthermore, patients with severe stenosis or regurgitation of the aortic/mitral valve and a large (>1.0cm) vegetation are considered to be high risk for embolization. However, small vegetations do embolize sometimes and can cause severe irreversible damage, especially in case of cerebral embolization. Transcranial doppler (TCD) technology which already exists for a long time and is especially used in neurophysiology, may help cardiologists in the detection of IE patients with high risk of cerebral embolization. TCD is able to detect micro embolic signals in the cerebral arteries, which may be a precursor signal of a larger embolization in the near future. This low cost and non-invasive diagnostic method can easily be implemented during the clinical stay of patients with confirmed IE and may be able to prevent irreversible neurological damage. However, data about the use of TCD in detection of embolization in patients with IE is yet to be demonstrated with future studies.

Photon Counting CT is an exciting new technology which will be more widely available in the near future. Benefits of this new technology in addition to the conventional CT is yielding optimal image contrast by counting high and low energy photons as equal contribution to the image signal. Furthermore, smaller detector pixels provide a far better spatial resolution and the intrinsic spectral sensitivity provides spectral information in every scan. With spectral imaging, it is possible to distinguish tissues and potentially identify specific characteristics of vegetations that are related to the change of embolization and or response to treatment.

These new ideas and perspectives can help clinicians in the diagnostic work up of patients with IE, and may revolutionize the future management of this catastrophic disease.

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List of Publications

This thesis

1. **Implementation of the 2015 European Society of Cardiology Guidelines for the Management of Infective Endocarditis in The Netherlands.** *A. R. Wahadat, J. W. Deckers, R. P. J. Budde, J. T. M. van der Meer, E. H. Natour, J. ten Oever, A. L. J. Kortlever-van der Spek, B. H. Stegeman, N. J. Verkaik, J. W. Roos-Hesselink & W. Tanis.* ***Neth Heart J. 2020 Dec;28(12):628-636. doi: 10.1007/s12471-020-01489-9.***

2. **The Impact of the Multidisciplinary Endocarditis Team on the Management of Infective Endocarditis.** *Ali R. Wahadat, Wilco Tanis, Tjebbe W. Galema, Laurens E. Swart, Wouter J. van Leeuwen, Nelianne J. Verkaik, Carolina A.M. Schurink, Bas van Dalen, Stieneke Zoet-Nugteren, Cihal Gurlek, Ricardo P.J. Budde, J.W. Roos-Hesselink.* ***Neth Heart J. 2022 Jul 4. doi: 10.1007/s12471-022-01707-6.***

3. **Heart team meetings during COVID-19.** *A.R. Wahadat, A.H. Sadeghi, W. Tanis.* ***Eur Heart J. 2020 May 21;41(20):1872-1874. doi: 10.1093/eurheartj/ehaa412.***

4. **Remote multidisciplinary heart team meetings in immersive virtual reality: a first experience during the COVID-19 pandemic.** *Amir H Sadeghi, Ali R Wahadat, Adem Dereci, Ricardo P J Budde, Wilco Tanis, Jolien W Roos-Hesselink, Hanneke Takkenberg, Yannick J H J Taverne, Edris A F Mahtab, and Ad J C Bogers.* ***BMJ Innov. 2021 Apr;7(2):311-315. doi: 10.1136/bmjinnov-2021-000662. Epub 2021 Mar 5.***

5. **Normal Imaging Findings after Aortic Valve Implantation on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography with Computed Tomography.** *Ali R Wahadat, Wilco Tanis, Asbjørn M Scholtens , Margreet Bekker, Laura H Graven, Laurens E Swart, Annemarie M den Harder, Marnix G E H Lam, Linda M de Heer, Jolien W Roos-Hesselink, Ricardo P J Budde.* ***J Nucl Cardiol. 2021 Oct;28(5):2258-2268. doi: 10.1007/s12350-019-02025-y. Epub 2020 Jan 23.***

6. **Normal imaging findings after ascending aorta prosthesis implantation on 18 F-Fluorodeoxyglucose Positron Emission Tomography with computed tomography.** *Ali R Wahadat, Wilco Tanis, Ties A Mulders, Laura H Graven, Margreet W A Bekker, Jos A Bekkers, Jolien W Roos-Hesselink, Ricardo P J Budde.* ***J Nucl Cardiol. 2021 Oct 27. doi: 10.1007/s12350-021-02826-0.***

7. **The additive value of semi-quantitative analysis of 18F-FDG PET/CT for the diagnosis of device related infections in patients with a Left Ventricular Assist Device.** *D. ten Hove, A.R. Wahadat, R.H.J.A. Slart, M. Wouthuyzen-Bakker, G. Mecozzi, K. Damman, H. Witteveen, K. Caliskan, O. Manintveld, B. Sinha, R.P.J. Budde, A.W.J.M. Glaudemans.* ***Submitted to the European Journal of Nuclear Medicine and Molecular Imaging.***

8. **Added value of 18 F-FDG-PET/CT and cardiac CTA in suspected transcatheter aortic valve endocarditis.** *Ali R Wahadat, Wilco Tanis, Laurens E Swart, Asbjørn Scholtens, Gabriel P Krestin, Nicolas M D A van Mieghem, Carolina A M Schurink, Tycho I G van der Spoel, Floris S van den Brink, Tessel Vossenberg, Riemer H J A Slart, Andor W J M Glaudemans, Jolien W Roos-Hesselink, Ricardo P J Budde.* ***J Nucl Cardiol. 2021 Oct;28(5):2072-2082. doi: 10.1007/s12350-019-01963-x. Epub 2019 Dec 2.***

9. **Screening for coronary artery disease in early surgical treatment of acute aortic valve infective endocarditis.** *Wiebe G Knol, Ali R Wahadat, Jolien W Roos-Hesselink, Nicolas M Van Mieghem, Wilco Tanis, Ad J C Bogers, Ricardo P J Budde.* ***Interact Cardiovasc Thorac Surg. 2021 Apr 19;32(4):522-529. doi: 10.1093/icvts/ivaa313.***

Outside this thesis

1. **Infective endocarditis in the Netherlands: current epidemiological profile and mortality: An analysis based on partial ESC EORP collected data.** S El Kadi, D M F van den Buijs, T Meijers, M D Gilbers, S C A M Bekkers, J P van Melle, R K Riezebos, W L Blok, W Tanis, A R Wahadat, J W Roos-Hesselink, T I G van der Spoel, S A J Chamuleau, O Kamp, EURO ENDO Investigators group. ***Neth Heart J. 2020 Oct;28(10):526-536. doi: 10.1007/s12471-020-01431-z.***

2. **Role of Cardiac CT in Infective Endocarditis: Current Evidence, Opportunities, and Challenges.** Mnahi Bin Saeedan, Tom Kai Ming Wang, Paul Cremer, Ali R Wahadat, Ricardo P J Budde, Shinya Unai, Gosta B Pettersson, Michael A Bolen. ***Radiol Cardiothorac Imaging. 2021 Feb 18;3(1):e200378. doi: 10.1148/ryct.2021200378.***

3. **Cardio-Room Rotterdam: Monthly Multidisciplinary Educational Meetings for Cardiac Surgery and Cardiology residents.** A.H Sadeghi, A. Dereci, R.Sakhi, R. Muslem, A.R. Wahadat, M. Arslan. **2020 EACTS newsletter; resident section.**

PhD-portfolio

Name PhD-Student	Ali Reza Wahadat
Department	Cardiology and Radiology
Research school	Cardiovascular Research School Erasmus MC (COEUR)
PhD-period	March 2018 – March 2021
Title thesis	Challenges in the Diagnostic Process and Management of Infective Endocarditis
Promotors	Prof. dr. J.W. Roos-Hesselink Prof. dr. R.P.J. Budde
Co promotor	Dr. W. Tanis
Date defense	18-10-2022

PhD Training	Year	Workload
General academic skills		
Basis Cursus Regelgeving en Organisatie voor Klinische Onderzoeken (BROK)	2018	1.5
Research Integrity	2018	0.3
In-depth courses (COEUR, NIHES, MOLMED)		
Arrhythmia Research Methodology, COEUR	2018	0.5
Biostatistical methods I: Basic principles, NIHES	2018	5.7
Heart Failure Research, COEUR	2018	0.5
Basic and Advanced Cardiac CT Course (5 days course)	2018	3.7
Intensive Care Part I and Part II, COEUR	2018	0.5
Pathophysiology of ischemic heart disease, COEUR	2018	0.8
Symposium of Medical Microbiology, UMCU, Utrecht, The Netherlands	2019	0.3
Cardiovascular Imaging and Diagnostics Part I, COEUR	2019	0.5
Basic and Advanced Cardiac CT Course (2 days of a 5 days course)	2019	1.4
Biomedical English Writing Course, Molmed	2019	0.4
Atrial Fibrillation, COEUR	2020	0.5
Aneurysmal disease, COEUR	2020	0.5
Congenital Heart Disease, COEUR	2021	0.5
Oral presentations		
European Association of Nuclear Medicine (EANM), Düsseldorf, Germany	2018	2.0
The Netherlands Society of Cardiology (NVVC), Arnhem, The Netherlands	2019	1.1
European Society of Cardiology EuroEcho, Vienna, Austria	2019	1.1

PhD Training	Year	Workload
Poster presentations		
European Society of Cardiology EuroEcho, Milan, Italy	2018	1.4
European Society of Cardiology (ESC), Amsterdam, The Netherlands (digital congress)	2020	1.9
Teaching activities/Supervising		
Education for residents in cardiology, Erasmus MC, Rotterdam, The Netherlands	2019	0.4
Education for PET/CT lab technicians, Erasmus MC, Rotterdam, The Netherlands	2019	0.4
Cardiac CT Course, case reading workshop on Cardiac CT, Prof. Dr. Budde, Erasmus MC, The Netherlands	2019	1.5
Education for residents in cardiology, Erasmus MC, Rotterdam, The Netherlands	2020	0.4
Education for residents in cardiology, Haga Hospital, The Hague, The Netherlands	2020	0.4
Supervising 2nd year medical students in writing a systematic review article	2020	0.5
Coordinating and moderating the Endocarditis Team discussions twice a week	2018-2021	10.0
Symposia, Seminar and workshops		
Workshop Advance Cardiovascular Life Support, Maasstad Hospital, The Netherlands	2018	0.5
Symposium Infective Endocarditis CVOI	2018	0.8
Symposium Infective Endocarditis CVOI	2020	0.8
Total workload (ECTS)		**40.8**

About the author | Curriculum Vitae

Ali Reza Wahadat was born on March 13th, 1991 in Kabul (Afghanistan). At the age of 9, he and his family fled the war in Afghanistan and settled in a small town (Hengelo) in Eastern part of The Netherlands. After graduating high school (Bataafse Lyceum, 2009 Hengelo), he studied biomedical science for one year at the University of Amsterdam. In 2010 he started medical school at Erasmus University Rotterdam and during this period he got involved in the field of cardiology by working in the Medical Student Team of the department of Cardiology of Erasmus Medical Center. After graduating in 2016 he worked for 14 months at the department of Cardiology of Maasstad Hospital in Rotterdam as a resident not in training (anios). In 2018 he started a research fellowship at the departments of Cardiology and Radiology of the Erasmus Medical Center Rotterdam and the department of Cardiology in Haga Hospital which resulted in this thesis: “Challenges in the Diagnostic Process and Management of Infective Endocarditis”, supervised by Prof. dr. R.P.J. Budde (promotor), Prof. dr. J.W. Roos-Hesselink (promotor) and dr. W. Tanis (Co-promotor). During his fellowship, he had the opportunity to present his work on national and international conferences and to publish his study results in several international peer reviewed medical journals.

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الحمد ا ... رب العالمين

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پدر و **مادر** عزیز، کلمات نمی توانند قدردانی من از شما را توصیف کنند، اما من یک تلاش کوچک انجام خواهم داد. فرار از کشور خودتان و پشت سر گذاشتن همه چیز و سپس شروع دوباره در یک کشور دیگر بسیار دشوار است. سفر به اینجا سخت و خطرناک بود. من همه اینها را به عنوان یک پسر ده ساله تجربه کردم، اما حالا متوجه می شوم که این کار چقدر باید برای شما دشوار بوده باشد. حالا که خودم پدر هستم، می فهمم که امنیت فرزندانم مهم ترین چیز است و .می خواهم از امنیتی که داده اید تشکر کنم. متشکرم از تمام حمایت ها و حرف های عاقلانه تان امیدوارم به من افتخار کنید و امیدوارم همیشه باعث افتخارتان باشم

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