Aus der Universitätsklinik für Infektiologie, Inselspital Bern

Chefarzt und Direktor: Prof. Dr. H. Furrer

Arbeit unter der Leitung von PD Dr. Parham Sendi

Infective endocarditis: What are predisposing conditions in native valves?

Inaugural-Dissertation zur Erlangung der Doktorwürde der Humanmedizin der Medizinischen Fakultät der Universität Bern

Vorgelegt von

Annina Elisabeth Büchi von Elgg/ZH

Und

Mario Hoffmann aus Deutschland

Von der Medizinischen Fakultät der Universität Bern auf Antrag der Dissertationskommission als Dissertation genehmigt.

Promotionsdatum:

Der Dekan der Medizinischen Fakultät

1 TABLE OF CONTENTS

2 List of Abbreviations

ΔP: Pressure difference

2D: Two-dimensional

3D: Three-dimensional

ACC/AHA: American College of Cardiology/American Heart Association

AI: Aortic valve insufficiency/regurgitation

ANOVA: Analysis of variance

AS: Aortic valve stenosis

AVA: Aortic valve area

AVAI: Aortic valve area index

BAV: Bicuspid aortic valve

CHD: Congenital heart disease

CI: Confidence interval

ECG: Electrocardiogram

ERO: Effective regurgitant orifice

ESC: European Society of Cardiology

GIM: General internal medicine

GUCH: Grown-up with congenital heart disease

HOCM: Hypertrophic obstructive cardiomyopathy

ICD: International Statistical Classification of Diseases and Related Health Problems

ICE: International Collaboration on Endocarditis

ICE-PCS: International Collaboration on Endocarditis-Prospective Cohort Study

IE: Infective endocarditis

IQR: Interquartile range

IVDU: Intravenous drug user

LA: Left atrium

LSIE: Left-sided infective endocarditis

LV: Left ventricle

LVOT: Left ventricular outflow tract

MI: Mitral valve insufficiency

MR: Mitral regurgitation

MRI: Magnetic resonance imaging

MS: Mitral valve stenosis

MVA: Mitral valve area

MVP: Mitral valve prolapse

N/A: Not available

NBTE: non-bacterial thrombotic endocarditis

NVIE: Native valve infective endocarditis

NYHA: New York Heart Association

PHT: Pressure half-time

PI: Pulmonary valve insufficiency/regurgitation

PS: Pulmonary valve stenosis

PVIE: Prosthetic valve infective endocarditis

PW: Pulsed wave

Q1: Question 1

Q2: Question 2

RF: Regurgitant fraction

RVol: Regurgitant volume

sPAP: Systolic pulmonary pressure

TDI: Tissue Doppler imaging

TI: Tricuspid valve insufficiency/regurgitation

TOE: Transoesophageal echocardiography

TS: Tricuspid valve stenosis

TTE: Transthoracic echocardiography

VC: Vena contracta

V_{max}: Maximum velocity

3 ABSTRACT

The term 'predisposing heart condition' is used as an indication of antimicrobial prophylaxis to prevent infective endocarditis (IE) and as a criterion for diagnosing IE according to the modified Duke criteria. Whereas the use of the term for antimicrobial prophylaxis is well defined, the criterion for diagnosing IE is not.

The general objective of this thesis is to narrow the definition of a predisposing heart condition in 'native' valves for the diagnosis of IE. Therefore, we reviewed the literature and the evidence about specific heart conditions reported to be a risk factor for IE. In parallel, we reviewed the imaging technique available at the time these studies were published and compared the results with imaging from today's perspectives and current definitions of a specific heart condition (i.e. valvular disease). Finally, we evaluated the knowledge and opinion of clinicians about the term predisposing heart condition.

Our literature review included 207 studies, the vast majority of which were descriptive. Only a few studies investigated valve pathology as a risk factor for IE via analytical statistics. In addition, three-quarters of all included studies involved patients who presented with IE prior to the publication of the modified Duke criteria.

Studies focussing on mitral valve prolapse (MVP, 116 publications), prior IE (96 publications), and bicuspid aortic valve (BAV, 78 publications) provided the most data. The odds ratio of developing IE for a patient who had previously experienced an episode of it was approximately 2.5. The mean proportion of patients with IE plus a history of previous IE was 8.3% (median 7.1%, interquartile range [IQR] 4.9%–10.2%). One study associated BAV with a higher risk of IE (hazard ratio 6.3). In 77 descriptive studies, a median of approximately 6% of patients with IE had BAV as an underlying condition. Our literature review on the evolution of imaging methods indicated, however, a considerable influence of medical progress on the diagnosis of MVP. Six analytical studies and 90 of the 110 descriptive studies included patients prior to the publication of the modified Duke criteria in 2000. For many years, MVP was diagnosed via auscultation only, and echocardiographic means for diagnosis were used in the late 90s. Therefore, both the risk of developing IE and the proportion of patients with IE and MVP as a predisposing factor could not be quantified.

The literature review on mitral valve stenosis (MS, 23 publications) and pathologies involving the pulmonary valve (18 publications) and the tricuspid valve (nine publications) provided little data. These publications had inconsistent results and low proportions of patients with IE had these valve pathologies.

The significance of aortic valve stenosis (AS, 46 publications), mitral valve insufficiency (MI, 41 publications), and aortic valve insufficiency (AI, 39 publications) as a predisposing heart condition was difficult to assess from today's perspective because of the progress made in imaging methods; of these studies, 75.6%, 78.6%, and 79.5%, respectively, included patients prior to the publication of the modified Duke criteria in the year 2000. In addition, except for AS (1989), the categorisation of mild, moderate, and severe valve pathology was established in 1998 or 2006. The publications had considerable heterogeneity with a wide distribution of results. An observational study indicated that with an increased incidence of AS, the risk of developing IE rises. Only one of these 126 publications for these three valve pathologies used analytical statistics. Congenital AS was associated with a higher risk of IE (hazard ratio of 4.9).

The results from the literature review parallel those from a survey that we performed to evaluate the knowledge and opinion of clinicians on the term predisposing heart condition. The survey indicated that there is significant uncertainty among clinicians regarding what is considered to be a Duke minor criterion for a predisposing heart condition in a native valve. The results from 318 questionnaires with responses from specialists in the fields of internal medicine, infectious diseases, and cardiology provided a wide range of answers. Their answers also showed that what the participants believed to be a current Duke minor criterion and what they thought should be a minor criterion had a median accordance of 33%.

Taken together, these findings demonstrate that there is uncertainty about what is considered a predisposing heart condition for the diagnosis of IE. This uncertainty is demonstrated in our extensive literature review and reflected in our survey among clinicians. The vast majority of studies used only descriptive statistics and included patients prior to the publication of the modified Duke criteria (2000). The tremendous progress in imaging methods and categorisation of valve pathologies since then makes it difficult to interpret the literature review analyses from today's perspective. Nonetheless, studies on MVP, a prior episode of IE, and BAV had the highest representation in the literature. Among these three pathologies, MVP is most likely to be affected by the evolution of imaging methods, and therefore its risk cannot be quantified. Sensitivity analyses and mathematical models performed on the data obtained in this systematic review may help to further narrow the definition of a predisposing heart condition.

4 INTRODUCTION

4.1 DEFINING A PREDISPOSING HEART CONDITION IN NATIVE VALVE IE

4.1.1 PATHOGENESIS

Intact vascular endothelium is thought to be protective against the invasion of bacteria. On the basis of histopathology and animal studies, it is presumed that the deposition of platelets and fibrin occurs spontaneously on 'abnormal' valve surfaces (e.g. endothelial lesions). A so-called non-bacterial thrombotic endocarditis (NBTE) is then formed. These locations serve as sites for the adherence of microorganisms during transient bacteraemia. The latter can arise spontaneously with chewing, tooth brushing, and other 'normal activities leading to skin lesions'.[6-9]

In the formation of NBTE, two major mechanisms seem to be important: first, an endothelial injury and second, a hypercoagulable state. NBTE predominantly occurs at the valve closure contact line on the atrial surfaces of the mitral and tricuspid valves and on the ventricular surfaces of the aortic and pulmonic valves. From a haemodynamic point of view, three circumstances may injure the endothelium, initiating NBTE:

1. A high-velocity jet striking the endothelium

2. Flow from a high-pressure to a low-pressure chamber

3. Flow across a narrow orifice at high velocity[6]

Bacteraemia with subsequent colonisation of the vegetation is the condition that converts NBTE to IE. The first inoculating bacteraemia can be clinically silent. Bacteria in the blood, which flows through a narrow orifice, will, e.g. precipitate at the low-pressure niches immediately beyond as a consequence of the Venturi effect. The damaged endothelium at these sites will allow adherence of the microorganisms.

Hence, the 'infectious' event in the pathogenesis of IE is bacterial adherence to damaged valves or endocardium during transient bacteraemia. The second step involves persistence and growth of bacteria within these lesions, usually associated with local extension and growing tissue damage.[10] Cytokines and pro-coagulant factors contribute to further enlargement of the infected coagulum, forming the well-known 'vegetation'.

The description of IE pathogenesis highlights the core question of this dissertation, namely whether or not an anatomical structure predisposes to infection in a clinically significant number of patients.

The detailed mechanisms of the host-pathogen interaction in IE are beyond the scope of this thesis. In brief, bacterial surface molecules (adhesins) mediate the adherence of microorganisms to the NBTE or to apparently intact valve endothelium. These adhesins are referred to as MSCRAMMs (microbial surface components recognising adhesive matrix molecules).[11] They bind to fibronectin, as has been shown for *Staphylococcus aureus* and viridans streptococci.[10] Other proteins include integrins of the β1 family. Pathogens possess fibronectin-binding proteins A and B (e.g. surface of *S. aureus*), or FimA (e.g. surface of viridans streptococci). The disease cascade is supported by an ongoing host response. Monocytes are attracted by particles released by the attached bacteria. They produce tissue factor and cytokines, which again triggers the coagulation pathway and attracts and activates blood platelets. Conceivably, the vegetation grows over the course of the disease.

4.1.2 Patients at Risk, Most Common Microorganisms, and Incidence

William Bart Osler (1849–1919) described endocarditis in a clinical context in 1885 in 'The Gulstonian Lectures on Malignant Endocarditis'.[12] The first description came from a French Renaissance physician, Jean François Fernel, approximately 350 years earlier and has been mentioned by several physicians at different medical events over the centuries.[13]

IE remains a challenging and important differential diagnosis for each clinician because of its high mortality and complication rates. In 2004, Moreillon et al. stated that the median incidence was 3.6 per 100,000 people per year (range 0.3–22.4) and ranged from ≤5 to ≥15 per 100,000 per year in individuals younger than 50 years and older than 65 years, respectively.[10] The male-to-female ratio was 2:1, and the median hospital mortality rate was 16% (range 11%–26%). However, the incidence of IE has not changed over the past three decades, despite improvements in health care.[10] This is most likely because a progressive change in risk factors for IE counterbalances the improvement in health care. Whereas in the pre-antibiotic era, the majority of patients with IE had a history of rheumatic heart disease, patients at risk nowadays include intravenous drug users (IVDUs); elderly people with degenerative valve disease; and patients with intravascular prostheses, with nosocomial disease, or who are undergoing haemodialysis. Staphylococci and oral streptococci account for most cases of IE. Together with enterococci, they are responsible for more than 80% of all cases.[10] In developing countries, *Streptococci* spp. remain the predominate causative agent of IE in rheumatic heart disease.[14]

Definite IE

- Direct evidence of infective endocarditis based on histology from surgery or autopsy, or on bacteriology (Gram stain or culture) of valvular vegetation or peripheral embolus.

Probable IE

- Persistently positive blood cultures (at least two blood cultures obtained, with two of two positive, three of three positive, or at least 70% of cultures positive if four or more cultures obtained) plus one of the following:
    - New regurgitant murmur, or
    - Predisposing heart disease (definite valvular or congenital heart disease or a cardiac prosthesis, excluding permanent pacemakers) and vascular phenomena (petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, and pulmonary, central nervous system, coronary, or peripheral emboli).
- Negative or intermittently positive blood cultures (any rate of blood culture positivity that does not meet the definition of persistently positive) plus all three of the following:
    - Fever
    - New regurgitant murmur, and
    - Vascular phenomena

Possible IE

- Persistently positive blood cultures plus one of the following:
    - Predisposing heart disease, or
    - Vascular phenomena
- Negative or intermittently positive blood cultures with all three of the following:
    - Fever
    - Predisposing heart disease, and
    - Vascular phenomena
- For viridans streptococcal cases only: at least two positive blood cultures without an extra-cardiac source, and fever

Rejected

- Endocarditis unlikely, alternate diagnosis generally apparent
- Endocarditis likely, empiric antibiotic therapy warranted
- Culture-negative endocarditis diagnosed clinically, but excluded by postmortem

Figure 1 – Definition of IE by von Reyn criteria[4]/'The Beth Israel Criteria', 1981

4.1.3 Development of The Duke Criteria

IE is difficult to diagnose and is determined in the presence of multiple findings.[1] Guidelines and diagnostic criteria have therefore been developed and are intermittently updated.[1]

Von Reyn et al. published the first criteria in 1981 (Figure 1, page 14) on the basis of 123 IE cases that were treated between 1970 and 1977.[4] The aim was to reduce mortality from IE through early recognition and treatment.[4]

As illustrated in Figure 1, predisposing heart conditions were recognised early. They included definite congenital or valvular heart disease or cardiac valve prosthesis.

The von Reyn criteria were rapidly accepted and widely used until new criteria, which included specific echocardiographic findings, were introduced by Durack et al. from the Duke Endocarditis Service in 1994.[3] The Duke criteria (Figure 2, page 15) emphasised the diagnostic tool of echocardiography. Major (Figure 3, page 17) and minor (Figure 4, page 18) criteria were proposed.

Definite IE

- Pathologic Criteria
    - Microorganisms: demonstrated by culture or histology in a vegetation, *or* in a vegetation that has embolized, *or* in an intracardiac abscess, *or*
    - Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
- Clinical criteria using specific definitions (listed in Figure 3 and Figure 4)
    - two major criteria, *or*
    - one major and three minor criteria, *or*
    - five minor criteria

Possible IE

- Findings consistent with IE that fall short of 'definite' but not 'rejected'

Rejected IE

- Firm alternate diagnosis for manifestations of endocarditis, *or*
- Resolution of endocarditis, with antibiotic therapy for 4 days or less, *or*
- No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

Figure 2 – Duke criteria[3] for IE

IE: infective endocarditis

They played a crucial role in defining definite and possible IE. The most important difference from the earlier definition was that the diagnosis of definite IE no longer required histological/pathological findings.

The term predisposing heart condition was adopted as a minor criterion under the topic 'predisposition'. Major and minor criteria were clinical criteria that used specific definitions. Predisposing conditions were related to a *JAMA* article from 1990. Dajani et al.[15] listed several cardiac conditions in which endocarditis prophylaxis was recommended:

- Prosthetic cardiac valves, including bioprosthetic and homograft valves
- Previous bacterial endocarditis, even in the absence of heart disease
- Congenital cardiac malformations
- Rheumatic and other acquired valvular dysfunction, even after valvular surgery
- Hypertrophic cardiomyopathy
- MVP with valvular regurgitation

Conditions in which endocarditis prophylaxis was NOT recommended included:

- Isolated secundum atrial septal defect
- Surgical repair (without residua beyond 6 months) of secundum atrial septal defect, ventricular septal defect, or patent ductus arteriosus
- Previous coronary artery bypass graft surgery
- MVP without valvular regurgitation
- Physiologic, functional, or innocent heart murmurs
- Previous Kawasaki disease without valvular dysfunction
- Previous rheumatic fever without valvular dysfunction
- Cardiac pacemakers and implanted defibrillators

Major Criteria

- Positive blood culture for infective endocarditis
    - Typical microorganism for infective endocarditis from two separate blood cultures
        - Viridans streptococci (including nutritional variant strains), *Streptococcus bovis*, HACEK group, *or*
        - Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, *or*
    - Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
        - Blood cultures drawn more than 12 hours apart, *or*
        - All three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart
- Evidence of endocardial involvement
    - Positive echocardiogram for infective endocarditis
        - Oscillating intracardiac mass, on valve or supporting structures, *or* 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, *or*
    - New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

Figure 3 – Major criteria as defined in Duke criteria[3]

In a population-based registry from Oregon (USA), Morris et al.[16] tried to determine the long-term incidence of endocarditis after repair of congenital heart defects in childhood. Included were individuals aged 18 years or younger who had surgical repair between 1958 and 1982. The analyses showed a continuing incidence of IE at 25 years after surgery, particularly for valvular AS, with a cumulative incidence of 13.3%. The investigators concluded that education about endocarditis prophylaxis for children and adults with repaired congenital heart defects is necessary. They underlined the importance of antibiotic prophylaxis because the number of adult survivors of corrected congenital heart defects will increase.

In 2000, another group from the Duke Endocarditis Service (Li et al.) proposed modifications of the old Duke criteria from 1994 (Figure 5, page 19; Figure 6, page 20; Figure 7, page 21).[1] On the basis of their analysis of more than 800 cases since 1984, the databases on echocardiography, and their experience with the Duke criteria in clinical practice, the most important adaptations were as follows. Possible IE should be defined as at least one major and one minor or three minor criteria. The term 'echocardiogram consistent with IE but not meeting major criterion' as a minor criterion was eliminated because of the widely used transoesophageal echocardiography (TOE) and its high informative value. Bacteraemia with a typical pathogen (*Staphylococcus aureus, Streptococcus bovis,* viridans streptococci*,* HACEK group) in patients who tested positive for Q-fever by serological testing or bacteriological proof of *Coxiella burnetti* in a single blood culture became major criteria.

Minor Criteria

- Predisposition: predisposing heart condition *or* intravenous drug use
- Fever: ≥38.0°C (100.4°F)
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
- Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with infective endocarditis
- Echocardiogram: consistent with infective endocarditis but not meeting major criterion as noted previously

Figure 4 – Minor criteria as defined in Duke criteria[3]

Definite IE

- Pathologic Criteria
    - Microorganisms: demonstrated by culture or histology in a vegetation, *or* in a vegetation that has embolized, *or* in an intracardiac abscess specimen, *or*
    - Pathologic lesions, vegetation, or intracardiac abscess confirmed by histology showing active endocarditis
- Clinical criteria using specific definitions (listed in Figure 6, page 20 and Figure 7, page 21)
    - two major criteria, *or*
    - one major and three minor criteria, *or*
    - five minor criteria

Possible IE

- one major criterion and one minor criterion, *or*
- three minor criteria

Rejected IE

- Firm alternate diagnosis for manifestations of endocarditis, *or*
- Resolution of endocarditis, with antibiotic therapy for 4 days or less, *or*
- No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less
- Does not meet criteria for possible IE, as above

Figure 5 – Definition of IE according to the modified Duke criteria[1]

IE: infective endocarditis

Major Criteria

- Positive blood culture for infective endocarditis
    - Typical microorganism for infective endocarditis from two separate blood cultures:
        - Viridans streptococci (including nutritional variant strains), *Streptococcus bovis*, HACEK group, or
        - *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 two positive cultures of blood samples drawn >12 hours apart, or
        - All three or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hour apart)
    - Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
- 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 change in pre-existing murmur not sufficient)

Figure 6 – Major criteria as defined in modified Duke criteria[1]

IE: infective endocarditis; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography

Minor Criteria

- Predisposition, predisposing heart condition, *or* intravenous drug use
- Fever, temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway's lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

Figure 7 – Minor criteria as defined by the modified Duke criteria[1]

IE: infective endocarditis

4.1.4 Antimicrobial Prophylaxis

Antibiotic prophylaxis of IE has been recommended for persons with predisposing cardiac conditions since 1955 by the American Heart Association (AHA).[17] Despite the lack of evidence, these guidelines were used for several decades. Duval et al. extrapolated the results of 2805 subjects to the French population and calculated the risk of developing IE as 1 in 46,000 for procedures without antimicrobial prophylaxis and as 1 in 150,000 for those with antimicrobial prophylaxis.[18]

Clinical evidence is still not sufficient to support antimicrobial prophylaxis.[14] Some guideline committees of several national cardiovascular societies re-evaluated the existing scientific evidence and independently drew four conclusions: [14]

1. The existing evidence does not support the extensive use of antibiotic prophylaxis recommended in previous guidelines.
2. Prophylaxis should be limited to the highest risk patients (patients with the highest incidence of IE and/or highest risk of adverse outcomes from IE).
3. The indications for antibiotic prophylaxis for IE should be reduced in comparison with previous recommendations.
4. Good oral hygiene and regular dental review are of particular importance for the prevention of IE.

4.1.5 Predisposing Heart Conditions

The term predisposing heart condition is stated in the latest modified Duke criteria from 2000 for the diagnosis of IE as a minor criterion, together with the term 'injection drug use'.[1] It was previously mentioned in the von Reyn criteria[4] as 'predisposing heart disease' under the topics probable and possible IE, as well as in the first Duke criteria from 1994,[3] also as a minor criterion.

In the literature of the 1970s and 1980s, several authors tried to define and elucidate underlying cardiac lesions in patients with IE and came to the conclusion that (i) rheumatic heart disease, (ii) MVP, (iii) congenital heart disease, and (iv) degenerative valve lesions predispose individuals to IE.[19-23] With the help of two-dimensional (2D) echocardiography, cardiologists were able to diagnose valve diseases such as MVP and degenerative calcified valve lesions, although, with the current diagnostic methods, the term 'degenerative valve lesions' includes a wide spectrum of valvular diseases.

In the Western world, the incidence of rheumatic heart diseases is decreasing, and hence, less frequently mentioned as a risk factor.

Among the above-mentioned predisposing heart conditions, the role of MVP became significant. In 1983, a study reported an incidence of MVP of 4%–6%.[21] In the hallmark case-control study by Clemens et al. in 1982,[20] individuals with MVP had an 8.2 higher risk of developing IE. However, it should be noted that from today's perspective, a diagnosis of MVP was made by either auscultatory or echocardiographic criteria. Auscultation – *before* the time when echocardiography was commonly available – was accepted for diagnosis and required the description of an apical late-systolic murmur and at least one systolic non-ejection click. Echocardiography was done in M-Mode and required ≥2 mm of pansystolic bowing or midsystolic buckling of the CD segment of the mitral tracing. The echocardiogram of 16% of the cases and 13% of the controls was not available for review. Patients with ruptured chordae tendineae were excluded.

4.1.6 Predisposing Heart Conditions from Today's Perspectives

When analysing the term predisposing heart condition from today's perspective, three parameters should first be reviewed to make the evaluation of a patient cohort meaningful.

1. What is the evidence for a specific heart condition putting a patient at risk of IE? The literature on this question is difficult to follow, and few analyses have tackled this question.
2. How is a specific heart condition diagnosed when it is being considered as a risk factor for IE? Over the past decades, the technology has improved significantly. Modern three-dimensional (3D) echocardiography and high-definition screens are available. Moreover, definitions on valvulopathies have changed over the last decades. Thus, it is important to align the evidence for a given heart condition with the corresponding imaging technique and definition at the time of a corresponding study. These findings should then be compared with today's perspectives.
3. In the guidelines on IE and the modified Duke criteria, the term predisposing heart condition is still not well defined. The European Society of Cardiology guidelines state that deficiencies remain and that modifications of the Duke criteria still await formal validation.[14] Moreover, they should be regarded as useful for classifying IE, but they do not replace clinical judgment. Nonetheless, a predisposing heart condition is mentioned as a minor criterion. Therefore, it plays a role in the daily routine of a clinician who has to decide which cardiac lesion is considered a predisposing heart condition. Hence, it is important to evaluate the knowledge and opinion of clinicians.

4.2 HISTORY – EVOLUTION OF ECHOCARDIOGRAPHY

1880: Pierre Curie and Jacques Curie: Discovery of piezoelectricity.[24]

1942: First A-Mode use in medicine by neurologist Karl Dussik for detecting lateral ventricles of the brain (first attempt to use ultrasound in medicine).[25]

1954 (technology first used in 1953): Carl Hellmuth Hertz (physicist from Lund University, Sweden) and Inge Edler (cardiologist from Sweden) published their first paper on 'The Use of Ultrasonic Reflectoscope for Continuous Movements of the Heart Wall' in which they described the use of M-Mode technology. Edler called the technique ultrasound cardiography.[26] The technology was initially used by Edler for the diagnosis of MS and MI.

1965: Harvey Feigenbaum first described pericardial effusion with ultrasound and M-Mode.[27]

1968: M-Mode was used to measure left ventricle (LV) dimensions (Feigenbaum).[28]

1973: 2D images were first reconstructed from M-Mode tracings by Gramiak (linear scanner).[29]

1973: First real-time, 2D scanner was developed by Bom et al.[30]

1973: Johnson et al. combined 2D with pulsed Doppler imaging to enable the detection of flow signals from specific locations within the heart or great vessels (duplex scanning).[31]

1974: Development of a hand-held transducer for 2D echocardiography by Griffith and Henry (sector scanner).[32]

1974: First 3D reconstruction of 2D images by Dekker et al.[33]

1975: First commercially successful mechanical scanner (B-Mode) by Eggleton.[34]

1976: Introduction of TOE by Frazin et al.[35]

1979/1980: Doppler ultrasound, first used by Holen[36] in 1979 and by Hatle[37] in 1980 with the modified Bernoulli equation to detect pressure gradients across stenotic valves, demonstrated that haemodynamic data could be accurately determined.

1980: TOE was first performed by putting a 2D transducer on a fiberoptic endoscope.[38]

1981: A phased-array ultrasound transducer was attached to the tip of a flexible gastroscope by Hanrath and colleagues.[39]

1982: PW-Doppler was introduced to measure transmitral blood flow velocities to assess LV diastolic function as the main clinical modality for non-invasive assessment of diastolic filling patterns.[40]

1983: Schlüter and Hanrath showed the clinical usefulness of TOE in adults.[41]

(1992–)1994: Tissue Doppler imaging was introduced to measure myocardial velocities.[155,156]

1992: The first 3D TOE was performed by using reconstruction techniques of 2D images.[42] The technique was applicable only to research.

2001/2003: First acquisition of 3D images in real time was reported.[43,44]

2004: Speckle tracking imaging (2D strain) was introduced to measure the shift of one marker (speckle) between two consecutive frames in a certain period.[45,46]

2012: First 3D echocardiography recommendations were published by the European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE).[47] In the 1960s, the idea of the 3D technique was developed and 3D scans of the heart were first reported in 1974 by Dekker et al. (see above).[33]

5 OBJECTIVES AND AIMS

Our general objective is to narrow the definition of a predisposing heart condition in native valves for the diagnosis of IE. We divided the objective into three specific aims:

1. To review the literature and the evidence on specific heart conditions reported to be a risk factor for IE.

2. To align the findings from the first aim with the imaging technique available at that time, as well as to theoretically compare, via extrapolation, the results of imaging from today's perspectives and current definitions of a specific heart condition (i.e. valvular disease).

3. To evaluate the knowledge and opinion of clinicians about the term predisposing heart condition.

6 METHODS

6.1 AIM 1 – LITERATURE REVIEW

A thorough literature review was conducted by searching Medline (http://www.ncbi.nlm.nih.gov/pubmed/). To identify relevant articles, the following keywords were defined: 'endocarditis', 'predisposing', 'predisposition', 'risk factor', 'heart condition'. The primary literature search was conducted in August 2015.
The following search strategy was used:

Endocarditis AND (predisposing OR predisposition OR risk factor OR heart condition)

Relevant articles cited by the articles identified in the search were tracked in the reference list of the corresponding article and, if relevant, also included. The retrieved articles were reviewed and the articles were included or excluded after screening for predefined criteria.

6.1.1 INCLUSION AND EXCLUSION CRITERIA

Conditions considered relevant for this study were as follows: prior endocarditis, AS or AI, BAV, MS or MI, MVP, pulmonary valve insufficiency (PI) or pulmonary valve stenosis (PS), and tricuspid valve insufficiency (TI) or tricuspid valve stenosis (TS).

Articles were first screened for language and year of publication. Only articles published after 1970 were included because von Reyn et al.[4] published criteria on the basis of IE cases that were treated between 1970 and 1977. Only articles published either in English or German were included.

The selection procedure was applied as follows:

1. If the title of the article indicated that the study did not concern adult humans or that it concerned diseases other than endocarditis or the cardiac conditions reviewed in this dissertation, the article was excluded.
2. If a publication did not contain any new patient group or did not match the aforementioned criteria in the abstract or full text, the article was excluded.

Data concerning the number of patients/cases included in the study, as well as patients with one of the diseases specifically described in this thesis, were extracted. Primary data analysis was conducted in Microsoft Excel 2013. Statistical analysis was conducted by using GraphPad Prism.

6.2 Aim 2 – Imaging Criteria

6.2.1 Definition of Valvulopathies

In order to find a valid definition of each valvulopathy, we screened all published American College of Cardiology/AHA (ACC/AHA) guidelines. Within these guidelines, references were tracked. In addition, a Medline (see above) search was conducted. The terms searched were the valve pathologies themselves: 'aortic stenosis', 'aortic insufficiency', 'bicuspid aortic valve', 'mitral stenosis', 'mitral insufficiency', 'mitral valve prolapse', 'tricuspid stenosis', 'tricuspid insufficiency', 'pulmonary stenosis', and 'pulmonary insufficiency'. Finally, definitions of valvulopathies were searched on the websites of the following journals: *Circulation*, *Journal of the American College of Cardiology (JACC)*, and *The New England Journal of Medicine (NEJM)*.

6.2.2 Evolution of Echocardiography

The search for papers in which milestones in echo technique were mentioned was conducted with MedLine (PubMed) and with an Internet-based search for the term 'evolution of echocardiography'. Given the fact that the search focussed on the historical perspective, we also used review articles to find reference articles. Thus, the search was not performed systematically, because the aim was to identify articles in which specific echo techniques were first mentioned.

6.3 AIM 3 – QUESTIONNAIRE

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

UNIVERSITÄT BERN

Universitätsklinik für Infektiologie
und
Universitätsklinik für Kardiologie

KNOWLEDGE AND OPINION STUDY ON

PREDISPOSING HEART CONDITIONS FOR INFECTIVE ENDOCARDITIS

I. Demographie des Befragten

Staatsexamen (Jahr):_____ Funktion (AA, OA, LA, CA, Praxis): _____

Arbeitsort : □ Universitätsspital □ Kantonsspital □ Regionalspital □ Praxis

FMH (Kardiologie, Innere Medizin, Infektiologie):

1. _____seit _____oder wird angestrebt seit _____
2. _____seit _____oder wird angestrebt seit _____
3. _____seit _____oder wird angestrebt seit _____

Gehört die Diagnostik oder Therapie der infektiösen Endokarditis u.a. zu Ihrer klinischen Tätigkeit?
□ Ja □ Nein

II. 4 Fragen

1. Gemäss den Duke – Kriterien gibt es das Minor Criterion for Infective Endocarditis „predisposing heart condition". **Was ist Ihres Wissens nach eine „predisposing heart condition"?** (*Sie können so viele Antworten aufschreiben, wie Sie wollen*).

_____

_____

_____

2. Sind die „predisposing heart conditions" einer nativen Klappe in den Amerikanischen oder Europäischen Guidelines für Endokarditis genau definiert?

□ Ja □ Nein □ weiss ich nicht.

3. Unabhängig von den Guidelines, welche Herzerkrankungen und/oder Valvulopathien sind Ihrer Meinung nach prädisponierend für eine Endokarditis auf einer nativen Klappe? (*Sie können so viele Antworten aufschreiben, wie Sie wollen*).

_____

_____

_____

4. Clemens et al. (*N Engl J Med 1982*; 307:776-781) beschrieb in einer case–control Studie (51 Patienten mit Endokarditis und 153 matched controls ohne Endokarditis), dass Patienten mit einem Mitralklappenprolaps ein deutlich höheres Risiko für eine Endokarditis haben, als Patienten ohne Mitralklappenprolaps (odds ratio 8.2; 95% CI 2.4 - 28.4). **Glauben Sie, dass die gleichen Ergebnisse resultieren, wenn die Studie heute wiederholt würde?** (mehrere Antworten möglich).

□ Ja, ähnliche Resultate.

□ Ja, aber die odds ratio würde weniger hoch ausfallen.

□ Nein, weil die heutigen Kriterien für einen Mitralklappenprolaps anders definiert sind, als sie dies 1982 waren.

□ Nein, weil die heutige Echokardiographie-Technik besser als 1982 ist, und damals der Mitralklappenprolaps überdiagnostiziert wurde.

□ Nein, weil die Resultate fast jeder kardiologischen Studie, die älter als 30 Jahre ist, nicht mehr angewendet werden können.

VIELEN DANK FÜR IHRE HILFE AN DIESER EVALUATION !

Figure 8 – Questionnaire

6.3.1 Questionnaire Design

The questionnaire (Figure 8, page 29) was designed and validated for the feasibility of completing it within 5 minutes. It was developed in conjunction with the Institute of Social and Preventive Medicine and Clinical Trials Unit (Bern University Hospital, Bern, Switzerland).

It included questions about the training, degrees, and clinical experience of the study participants, as well as two knowledge and two opinion questions. We visited 19 departments in 13 different institutions within Switzerland to perform the survey (see 6.3.2 Study Participants, page 30). Questionnaires were distributed at morning meetings and collected directly afterwards. All questionnaires were filled out anonymously. A sample size of 300 was targeted prior to the study. Participants included either physicians undergoing postgraduate education and specialisation, or specialists in the fields of internal medicine, infectious diseases, or cardiology. Answers were independently evaluated by two members of the study team and categorised as acceptable (wide range of answers) or definitely wrong (narrow range of answers). The rationale to accept a wide range of answers relied on the fact that the term predisposing heart condition in native valves is not well defined; thus, for many answers, it was scientifically difficult to categorise them as definitely wrong. In case of disagreement, a third member of the study team was involved and the decision was made by the majority. Accordance between knowledge and opinion was analysed and illustrated in a bidirectional graph. For this analysis, foreign body material was excluded because the focus in the opinion question was on native valves, whereas 'foreign body material' was a correct answer in the knowledge question. GraphPad Prism 5.0 was used for statistical analysis. Differences in group proportions were assessed by contingency tables and the chi-square test, or by Fisher's exact probability test if cell values were less than 5. The Student's t-test was applied where appropriate. A two-tailed p-value of 0.05 or less was considered significant.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the study.

6.3.2 Study Participants

The questionnaires were distributed at lectures and meetings. The following institutions were included:

- Department of General Internal Medicine, Bern University Hospital, Bern, Switzerland
- Department of Intensive Care Medicine, Inselspital, Bern University Hospital, Bern, Switzerland

- Department of Infectious Diseases, University Hospital Bern and University of Bern, Switzerland
- Department of Cardiology, Swiss Cardiovascular Center, University Hospital, Bern, Switzerland
- Department of Cardiology, Kantonsspital, Aarau, Switzerland
- Department of Cardiology, Luzerner Kantonsspital, Lucerne, Switzerland
- Department of Cardiology, Triemlispital, Zurich, Switzerland
- Department of Internal Medicine, University Hospital Basel, Switzerland
- Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital Basel
- Division of Infectious Diseases, Kantonsspital, St. Gallen
- Clinic of Internal Medicine, Bürgerspital, Solothurn, Switzerland
- Clinic of Cardiology, Kantonsspital, Olten, Switzerland
- Division of Cardiology, Department of Internal Medicine, Kantonsspital Winterthur, Winterthur, Switzerland
- Department of Internal Medicine, Spitäler FMI, Interlaken, Interlaken, Switzerland
- Department of Internal Medicine, Regionalspital Emmental, Burgdorf, Burgdorf, Switzerland
- Department of Internal Medicine, Regionalspital Emmental, Langnau, Langnau i.E., Switzerland
- Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital Baselland, University of Basel, Basel, Switzerland

7 Results

7.1 Literature Review

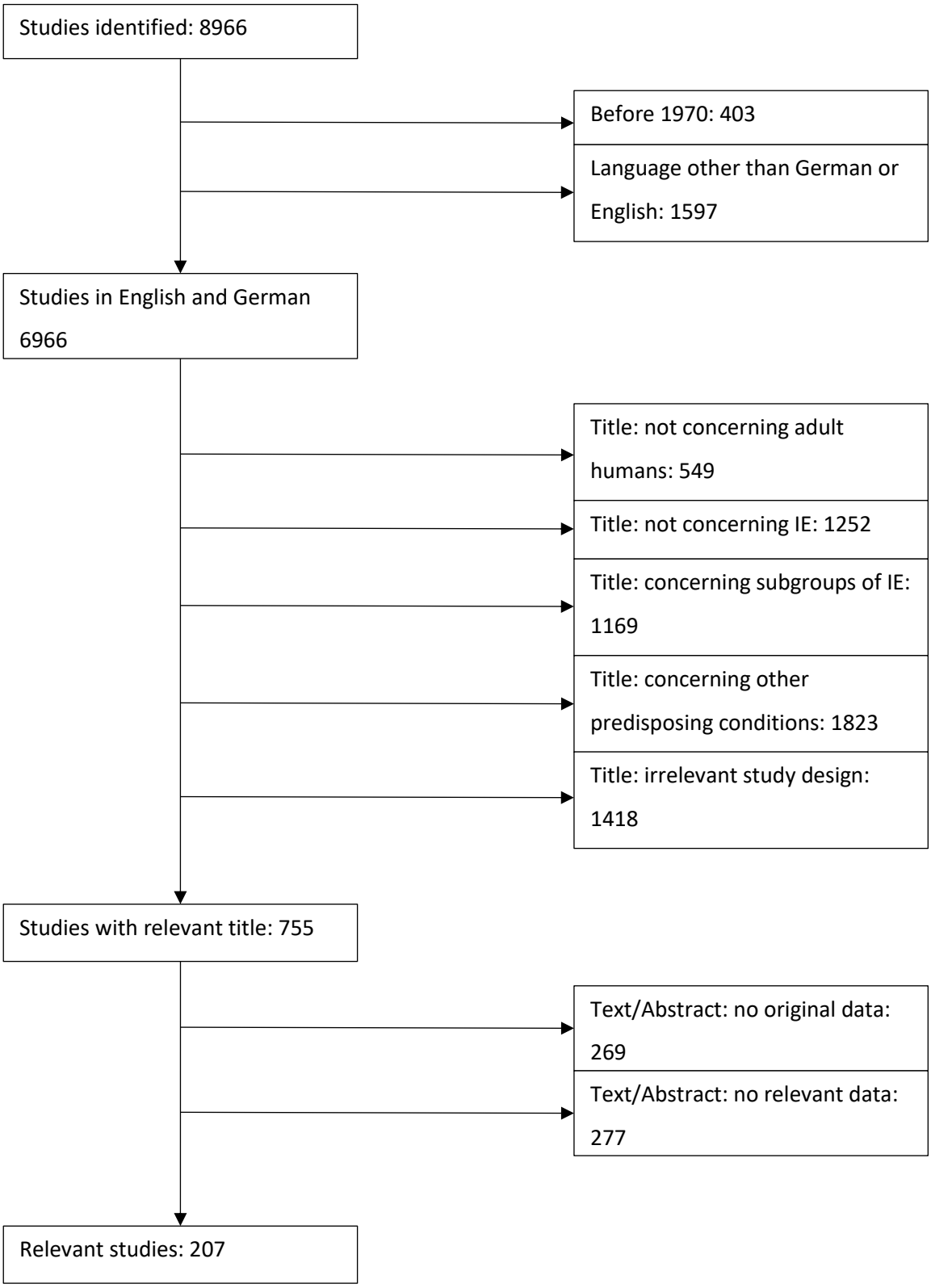

Figure 9 – Algorithm for literature review

7.2 Definition of Valvulopathies and Method Imaging

Specific definitions of valvulopathies were published by ACC/AHA first in 1998, followed by guidelines in 2006 and 2014. Results regarding the definition of valvulopathies and imaging methods are combined in an overview in the next sections.

7.3 Prior IE

Of the 207 studies considered relevant in the literature review, 91 mentioned prior IE.

7.3.1 Publications That Included Analytical Statistics

Strom et al.[9] reviewed 279 cases of IE from 1988 to 1990 from 54 hospitals in Delaware Valley (USA). Compared with that of the controls, the odds ratio for developing IE with prior IE in these cases was 35.2.

Todd et al.[48] described a study of 29 patients with echocardiographically confirmed IE and 79 controls (with echocardiograms) from 2002 to 2004 in the UK. They reported that a patient with a history of IE had an odds ratio of 2.2 (95% confidence interval [CI] 0.4–10.3, p-value 0.383) for developing IE.

Alagna et al.[49] reported the results of a study of 1874 patients from the International Collaboration on Endocarditis cohort from 2000 to 2006 with a 1-year follow-up. Prior IE had a reported odds ratio of 2.8 (95% CI 1.5–5.1) for causing IE.

7.3.2 Prior IE – Publications with Descriptive Statistics

Reference	Time	Place	Cases of (NV)IE	Cases with Prior IE	% with Prior IE	Study Design
Pelletier[50]	1963–1972	USA	125	20	16.0%	Retrospective review of patient charts, multicentre
Pedersen[51]	1944–1973	Denmark	80	3	3.8%	Retrospective, single centre
Garvey[52]	1968–1974	USA	154	12	7.8%	Retrospective analysis of patient records, autopsy files, and files of the infectious diseases department
Lowes[53]	1966–1975	UK	60	1	1.7%	Retrospective survey, single centre
Welton[54]	1967–1976	USA	96	18	18.8%	Retrospective, single centre
Haddy[55]	1964–1979	USA	66	4	6.1%	Retrospective, single centre
Hammel[56]	1971–1980	Switzerland	31	9	29.0%	Single centre, not indicated whether prospective or retrospective
Venezio[57]	1972–1980	USA	32	2	6.3%	Retrospective, single centre
Bayliss[58]	1981–1982	UK	541	34	6.3%	Retrospective, multicentre (British Isles)
Terpenning[59]	1976–1985	USA	154	6	3.9%	Retrospective review of patient charts, multicentre
King[60]	1985–1986	USA	75	8	10.7%	Prospective, multicentre
Steckelberg[61]	1970–1987	USA	697	105	15.0%	Retrospective from prospectively collected records, multicentre (comparison of a population- based cohort vs. cohort of Mayo Clinic)
Kim[62]	1975–1987	USA	56	2	3.6%	Retrospective, single centre
Varstela[63]	1976–1987	Finland	58	3	5.2%	Retrospective, single centre
Jaffe[64]	1983–1988	USA	70	9	12.9%	Retrospective review, single centre
Hogevik[65]	1984–1988	Sweden	98	14	14.0%	Prospective non-randomised, single centre
Van der Meer[8]	1986–1988	Netherlands	349	30	8.6%	Prospective epidemiologic study, multicentre
Nissen[66]	1980–1989	Denmark	132	5	3.8%	Retrospective, multicentre
Schon[67]	1980–1989	Germany	51	7	13.7%	Retrospective, single centre

Gentry[68]	1983–1989	USA	54	15	28.0%	Retrospective review, single centre
Watanakunakorn[69]	1980–1990	USA	181	13	7.2%	Retrospective 1980–1985, prospective 1986–1990, single centre
Strom[9]	1988–1990	USA	279	17	6.1%	Population-based, case-control study, multicentre
Roberts[70]	1954–1991	USA	104	4	3.8%	Retrospective, multicentre
Delahaye[71]	1990–1991	France	415	46	11.0%	Prospective survey, multicentre
Selton-Suty[72]	1990–1991	France	297	19	6.4%	Prospective, multicentre
Tornos[73]	1975–1992	Spain	194	12	6.2%	Prospective observational, single centre
Rognon[74]	1983–1993	Switzerland	179	19	10.6%	Retrospective, multicentre
Sandre[75]	1985–1993	Canada	80	4	5.0%	Retrospective review, single centre
Werner[76]	1989–1993	Germany	106	2	1.6%	Retrospective, single centre
Ferreiros[77]	1992–1993	Argentina	294	30	10.2%	Prospective registry, multicentre
Weng[78]	1984–1994	Taiwan	109	2	1.8%	Retrospective, single centre
Lamas[79]	1985–1996	UK	100	4	4.0%	Prospective, single centre
Bouza[80]	1994–1996	Spain	109	17	15.6%	Prospective observational case series, single centre
Castillo[81]	1987–1997	Spain	95	2	2.0%	Prospective case series, single centre
Mouly[82]	1997–1998	France	90	8	9.0%	Retrospective observational, single centre
Abramczuk[83]	1988–1998	Poland	152	7	4.9%	Retrospective, single centre
Cetinkaya[84]	1974–1999	Turkey	228	5	2.2%	Retrospective (hospital charts) review, single centre
Fefer[85]	1990–1999	Israel	108	7	9.0%	Retrospective (medical records), single centre
Pachirat[86]	1990–1999	Thailand	203	4	2.0%	Single centre, combined retrospective and prospective data collection
Tleyjeh[87]	1970–2000	USA	107	8	7.0%	Retrospective (population-based survey), multicentre
Netzer[88]	1980–2000	Switzerland	212	9	4.2%	Retrospective review of clinical records, single centre

Alestig[89]	1984–2000	Sweden	98	14	14.0%	Prospective clinical studies carried out in Göteborg since 1984, data obtained from a Swedish national registry of IE since 1995 and existing literature
Gotsman[90]	1991–2000	Israel	100	22	22.0%	Retrospective, single centre
Koegelenberg[91,92]	1997–2000	South Africa	47	1	2.1%	Prospective observational study, single centre
Castillo[93]	1987–2001	Spain	154	3	2.0%	Prospective observational, multicentre
Moura[94]	1989–2001	Portugal	69	6	8.0%	Retrospective, single centre
Yoshinaga[95]	1997–2001	Japan	239	15	6.3%	Retrospective observational cohort study, multicentre (66 institutes)
Chu[96]	1997–2002	New Zealand	65	5	7.7%	Retrospective, single centre
Yousuf[97]	2000–2002	Malaysia	45	10	22.2%	Retrospective analysis of case records, single centre
Ferreiros[77]	2001–2002	Argentina	470	53	11.3%	Prospective, multicentre
Cicalini[98]	1980–2003	Italy	267	38	13.4%	Retrospective (patient records), single centre
Nashmi[99]	1993–2003	Saudi Arabia	47	3	6.4%	Retrospective, single centre
Hsu[100]	1995–2003	Taiwan	315	22	7.0%	Retrospective review, single centre
Jain[101]	1996–2003	USA	247	42	17.0%	Retrospective, single centre
Hill[102]	2000–2004	Belgium	203	24	12.0%	Prospective observational cohort study, single centre
Giannitsioti[103]	2000–2004	Greece	195	19	9.7%	Prospective cohort study, multicentre
Benito[104]	2000–2005	ICE cohort	1622	58	3.6%	Prospective cohort study, multicentre (data from the ICE-PCS)
Murdoch[105]	2000–2005	ICE cohort	2781	222	8.0%	Prospective cohort study, multicentre (ICE-PCS)
Walls[106]	2000–2005	ICE cohort	336	34	10.1%	Prospective cohort, multicentre
Correa de Sa[107]	1970–2006	USA	150	14	9.3%	Retrospective, multicentre
Galvez-Acebal[108]	1984–2006	Spain	705	57	8.0%	Observational multicentre study
Pazdernik[109]	1998–2006	Czech Republic	106	5	4.7%	Retrospective, single centre

Alagna[49]	2000–2006	ICE cohort	1783	135	7.4%	Prospective, multicentre
Tugcu[110]	1997–2007	Turkey	28	2	7.1%	Retrospective review, single centre
Mokhles[111]	1998–2007	Netherlands	138	18	13.0%	Retrospective observational cohort study, single centre
Baskerville[112]	2002–2007	Australia	89	13	14.6%	Retrospective review (medical records), multicentre
Wong[113]	2002–2007	New Zealand	57	5	9.0%	Retrospective review, single centre
Khaled[114]	2006–2007	Yemen	72	1	1.4%	Prospective, single centre
Mokhles[115]	2001–2008	Netherlands	191	27	14.1%	Retrospective observational cohort study, single centre
Nunes[116]	2001–2008	Brazil	62	14	23.0%	Prospective, single centre
Erbay[117]	2004–2008	Turkey	107	10	9.3%	Retrospective, single centre
Dzupova[118]	2007–2008	Czech Republic	134	8	6.0%	Prospective, multicentre
Selton-Suty[119]	2008	France	497	32	6.4%	Prospective population-based observational study, multicentre
Nomura[120]	1996–2009	Japan	62	3	5.0%	Retrospective, single centre
Fernandez-Hidalgo[121]	2000–2009	Spain	337	17	5.0%	Prospective observational cohort study, single centre
Leone[122]	2004–2009	Italy	753	33	4.4%	Prospective, multicentre
Wu[123]	2004–2009	Taiwan	205	5	2.4%	Retrospective, single centre
Knudsen[124]	2007–2009	Denmark	147	8	5.4%	Prospective, single centre
Knudsen[125]	2007–2009	Denmark	149	9	6.0%	Prospective, single centre
Ferraris[126]	2003–2010	Italy	111	12	10.8%	Retrospective, single centre
Poesen[127]	2003–2010	Belgium	88	8	9.1%	Retrospective, single centre
Gupta[128]	2005–2010	India	83	5	8.2%	Retrospective, single centre
Mirabel[129]	2005–2010	New Caledonia	51	4	7.8%	Retrospective, single centre
Koeda[130]	1997–2011	Japan	119	7	5.9%	Retrospective, single centre
Fernandez-Hidalgo[131]	2000–2011	Spain	438	7	2.9%	Prospective observational cohort study, single centre
Ferreira[132]	2000–2011	Portugal	147	5	3.4%	Retrospective, multicentre (2 hospitals)

Rizzi[133]	2004–2011	Italy	1056	55	5.2%	Retrospective analysis of a multicentre, prospective observational cohort study
Korem[134]	2009–2011	Israel	37	2	5.4%	Prospective observational study, single centre
Turak[135]	2009–2011	Turkey	122	11	9.0%	Retrospective, single centre
Chu[136]	2008–2012	ICE-PLUS cohort	1296	100	7.8%	Prospective cohort study, multicentre (ICE-PLUS cohort)
Olmos[137]	1996–2013	Spain	1122	88	7.8%	Prospective, multicentre
Simsek-Yavuz[138]	2000–2013	Turkey	325	18	5.5%	Prospective 102 cases (first 5 years) and retrospective 223 cases thereafter, single centre
Fukuchi[139]	2008–2013	Japan	82	2	2.4%	Prospective, multicentre
Gupta[140]	2010–2013	India	109	8	7.3%	Retrospective, single centre

Table 1 – Literature for prior IE

ICE: International Collaboration on Endocarditis; ICE: International Collaboration on Endocarditis; ICE-PCS: International Collaboration on Endocarditis-Prospective Cohort Study; IE: infective endocarditis; NVIE: native valve infective endocarditis

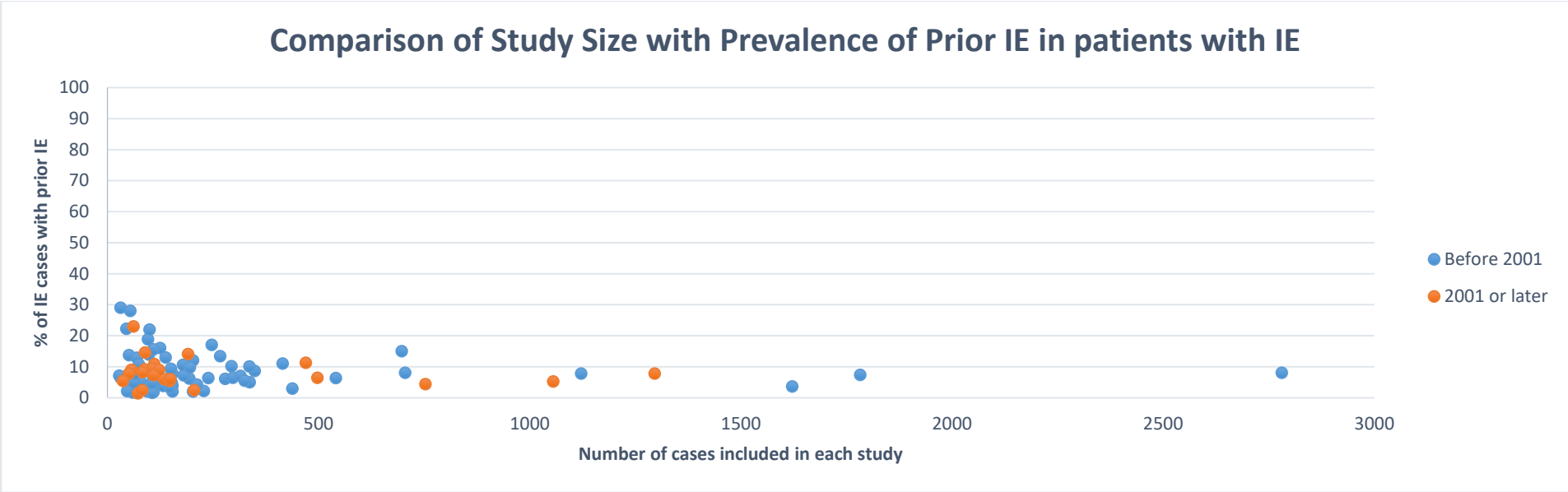

Figure 10 – Comparison of study size with prevalence of prior IE in patients with IE and in association with IE criteria prior to and after modified Duke criteria

IE: infective endocarditis

7.3.3 Summary of Results: Prior IE

We identified three studies showing that a history of IE was associated with a higher risk of a second episode of IE. While two studies showed an odds ratio of approximately 2.5,[48,49] one calculated an odds ratio of >35.[9] Considering the overview of the results, we postulate that the odds ratio in that study was overrated.

Ninety-five studies were identified that published descriptive statistics on the proportion of patients with a history of IE in newly diagnosed IE cases. Of these studies, 23 (24.2%) included patients in the study after the publication of the modified Duke criteria. A two-tailed t-test of the number of publications before and after 2001 was highly significant, with a p-value of <0.0001. The mean number of patients included in the 95 studies was 263 (median 122, IQR 80–239), in the studies prior to 2001 was 264 (median 128.5, IQR 80–245), and in the studies after 2001 was 259 (median 111, IQR 82.5–198). Of the 95 studies, the mean proportion of patients with IE plus a history of previous IE was 8.3% (median 7.1%, IQR 4.9%–10.2%). The mean proportion of patients with IE plus a history of previous IE in studies prior to 2001 was 8.4%, the median was 7%, and the IQR was 4.3%–10.5%. After 2001, the numbers were as follows: mean 8.1%, median 7.8%, IQR 5.4%–9.2%. These differences were not significant in an unpaired t-test. These results are in line with the dot plot that compares the study size with the prevalence of prior IE in patients with IE and in association with IE in accordance with primary and modified Duke criteria. The strongest cluster was seen between the prevalence lines 5% to 10%. Studies with small sample sizes and above the prevalence line of 15% indicated a publication bias, whereas studies with large sample sizes (e.g., >700 patients) confirmed the 5% to 10% estimate.

In the preliminary meta-analysis, the proportion of patients with IE and prior IE as an underlying condition was 6.9% (95% CI 6.5%–7.2%) in a fixed effects model and 7.4% (95% CI 6.5%–8.2%) in a random effects model. As a few studies contributed greatly to the overall heterogeneity, a second meta-analysis with stricter clinical inclusion/exclusion criteria is planned.

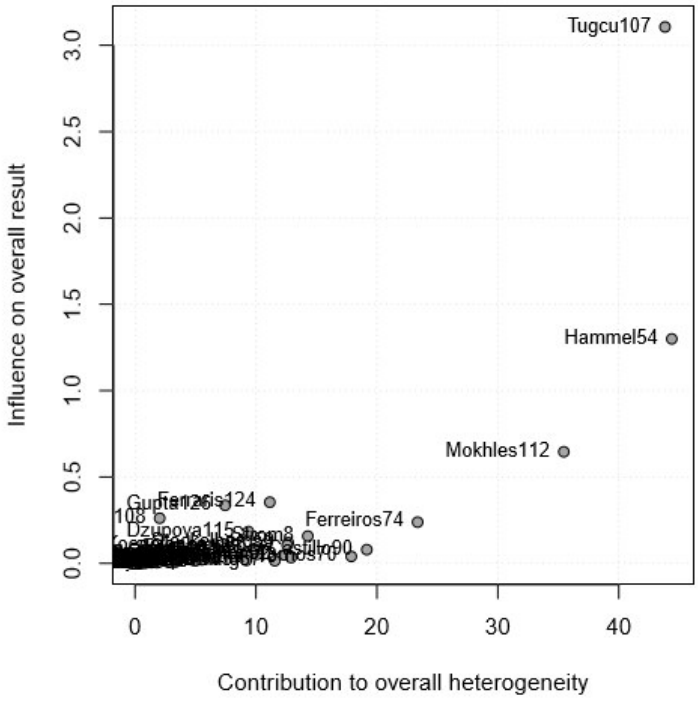

Figure 11 – Contribution of studies to overall heterogeneity for prior IE

IE: infective endocarditis

7.4 Aortic Valve

7.4.1 Aortic Valve Stenosis (AS)

Of the 207 articles considered relevant after the literature review, 46 mentioned AS.

7.4.1.1 Analytical Statistics

In 2011, Verheugt et al.[141] described patients from the CONCOR national registry for adults with congenital heart disease from the Netherlands. Of 922 patients with congenital AS, 26 (2.8%) developed IE. This equals a hazard ratio of 4.9 (95% CI 2.2–10.5).

7.4.1.2 Descriptive Statistics

Gersony et al.[142] described 462 patients with AS from the Second Natural History Study of Congenital Heart Defects conducted in the USA between 1958 and 1965. They reported a prevalence rate of 21.6 per 10,000 patients (95% CI 0.5–120.6). Follow-up was conducted for 8115 person-years; patients with conservative management had an incidence rate of 15.7 per 10,000 person-years (95% CI 6.3–32.4). Patients with a peak systolic gradient of ≥50 mmHg had an incidence rate of 54.4 per 10,000 person-years (95% CI 33.2–84.1), and patients with a peak systolic gradient of <50 mmHg had an incidence rate of 4.5 per 10,000 person-years (95% CI 0.6–16.4). The investigators stated that only the severity of AS is related to the occurrence of IE.

Reference	Time	Place	Patients with (NV)IE	Cases with AS	% with AS	Study Design
Keane[143]	1958–1965	USA	462.0	14	3.0%	Prospective cohort study, multicentre
Pelletier[50]	1963–1972	USA	125.0	25	20.0%	Retrospective review of patient charts, multicentre
Thell[144]	1960–1974	USA	42.0	6	14.3%	Retrospective (pathology samples), multicentre
Lowes[53]	1966–1975	UK	60.0	4	6.7%	Retrospective survey, single centre
Robbins[145]	1970–1977	USA	56.0	7	12.5%	Retrospective, single centre
Grossman[146]	1951–1979	Israel	228.0	21	9.2%	Retrospective, single centre
Venezio[57]	1972–1980	USA	32.0	3	9.4%	Retrospective, single centre
Rudolph[147]	Before 1983	Germany	50.0	11	22.0%	Single centre, probably prospective
Terpenning[59]	1976–1985	USA	154.0	1	0.6%	Retrospective review of patient charts, multicentre
Hodes[148]	1977–1985	Ethiopia	51.0	1	2.0%	Retrospective, single centre
Mansur[149]	1978–1986	Brazil	287.0	6	2.1%	Retrospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349.0	9	3.5%	Prospective epidemiologic study, multicentre
Nissen[66]	1980–1989	Denmark	132.0	8	6.1%	Retrospective, multicentre
Thamlikitkul[150]	1982–1989	Thailand	75.0	14	13.3%	Retrospective, single centre
Roberts[70]	1954–1991	USA	96.0	25	26.0%	Retrospective, multicentre
Choudhury[151]	1981–1991	India	186.0	2	1.1%	Retrospective, single centre
Delahaye[71]	1990–1991	France	415.0	14	3.4%	Prospective survey, multicentre
Benn[152]	1984–1993	Denmark	62.0	6	9.7%	Retrospective, multicentre
Sandre[75]	1985–1993	Canada	80.0	2	2.5%	Retrospective review, single centre
Werner[76]	1989–1993	Germany	106.0	8	7.5%	Retrospective, single centre
Netzer[153]	1980–1995	Switzerland	212.0	28	13.0%	Retrospective, single centre
Lamas[79]	1985–1996	UK	100.0	7	7.0%	Prospective, single centre
Dyson[154]	1987–1996	UK	78.0	2	2.6%	Retrospective, single centre
Castillo[81]	1987–1997	Spain	95.0	8	8.0%	Prospective case series, single centre
Cheng[155]	1994–1999	Australia	40.0	1	2.5%	Retrospective, multicentre
Di Filippo[156]	1966–2001	France	153.0	1	0.6%	Retrospective, single centre

Castillo[93]	1987–2001	Spain	154.0	18	11.5%	Prospective observational, multicentre
Tariq[157]	1988–2001	Pakistan	159.0	2	1.3%	Retrospective, single centre
McKay[158]	1989–2001	New Zealand	29.0	2	6.9%	Retrospective, multicentre
Tariq[159]	1997–2001	Pakistan	66.0	2	3.0%	Retrospective, single centre
Cecchi[160]	2000–2001	Italy	67.0	5	7.5%	Prospective, multicentre
Chu[96]	1997–2002	New Zealand	65.0	8	12.3%	Retrospective, single centre
Durante-Mangoni[161]	2000–2005	ICE cohort	2759.0	N/A	10%–28%	Prospective, multicentre (ICE cohort)
Assiri[162]	2002–2007	Saudi Arabia	44.0	2	4.5%	Retrospective, single centre
Wong[113]	2002–2007	New Zealand	57.0	5	9.0%	Retrospective review, single centre
Mokhles[115]	2001–2008	Netherlands	191.0	2	1.0%	Retrospective observational cohort study, single centre
Dzupova[118]	2007–2008	Czech Republic	134.0	4	3.0%	Prospective, multicentre
Leone[122]	2004–2009	Italy	753.0	20	2.7%	Prospective, multicentre
Nakatani[163]	2007–2009	Japan	513.0	37	7.2%	Prospective survey, multicentre
Marks[164]	1998–2010	UK	336.0	3	0.9%	Retrospective observational cohort study, single centre
Cecchi[165]	2007–2010	Italy	677.0	26	3.8%	Prospective, multicentre
Ma[166]	2002–2011	China	115.0	8	7.0%	Single centre
Begezsan[167]	2007–2011	Romania	45.0	5	11.1%	Retrospective, single centre
Collins[168]	2008–2011	USA	95.0	5	5.3%	Prospective observational, single centre
Verheugt[141]	Before 2011	The Netherlands	922.0	26	2.6%	Prospective cohort study, multicentre

Table 2 – Literature for AS: People with IE with AS as an underlying condition

AS: aortic valve stenosis; ICE: International Collaboration on Endocarditis; N/A: not available; NVIE: Native valve infective endocarditis

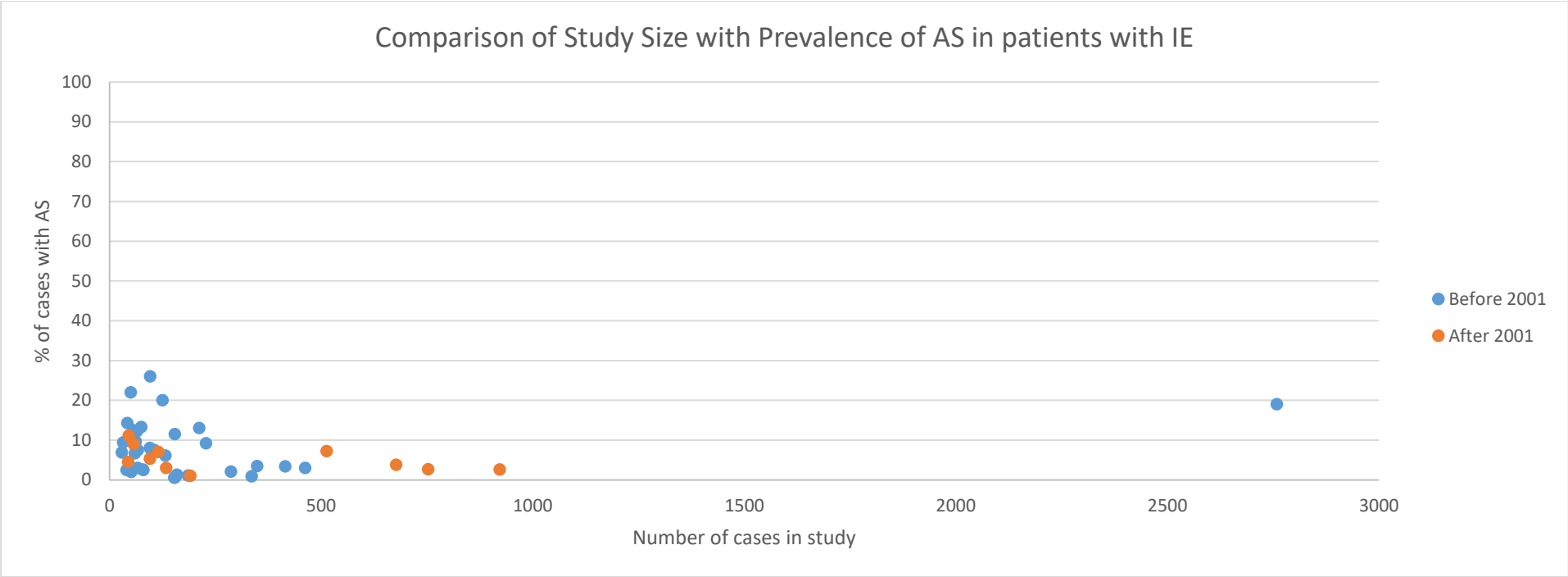

Figure 12 – Comparison of study size with prevalence of AS in patients with IE and in association with IE criteria prior to and after modified Duke criteria

AS: aortic valve stenosis; IE: infective endocarditis

7.4.1.3 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Keane[143]	1958–1965	M-Mode (1954)[26]	
Pelletier[50]	1963–1972		Severe: Conn et al. 1971[169]: AVA ≤ 0.5 cm^2 Rapaport et al. 1975[170]: AVA ≤ 1.0 cm^2
Thell[144]	1960–1974		
Lowes[53]	1966–1975		
Robbins[145]	1970–1977	+ B-Mode (2D (1975))[34]	
Grossman[146]	1951–1979	+ Doppler (CW (1979))[36,37]	
Venezio[57]	1972–1980		Chizner et al. 1980[171]: Moderate: AVA 0.71–1.09 cm^2, peak ΔP ≤ 70 mmHg
Rudolph[147]	Before 1983		
Terpenning[59]	1976–1985	+ PW (1982),[40] TOE (1983)[41]	
Hodes[148]	1977–1985		
Mansur[149]	1978–1986		
Van der Meer[8]	1986–1988		Horstkotte et al. 1988[172]: Mild: AVA > 1.5 cm^2 Moderate: AVA 0.8–1.5 cm^2, peak ΔP ≤ 80 mmHg
Nissen[66]	1980–1989		Rahimtoola et al. 1989[173]: Mild: AVA > 1.5 cm^2, AVAI > 0.9 cm^2/m^2 Moderate: AVA 1.1–1.5 cm^2, AVAI ≥ 0.6–0.9 cm^2/m^2 Severe: AVA ≤ 0.8–1.0 cm^2, AVAI ≤ 0.4–0.6 cm^2/m^2
Thamlikitkul[150]	1982–1989		
Roberts[70]	1954–1991		
Choudhury[151]	1981–1991		
Delahaye[71]	1990–1991		
Benn[152]	1984–1993		
Sandre[75]	1985–1993		
Werner[76]	1989–1993		
Netzer[153]	1980–1995	+ TDI (1994)[174,175]	
Lamas[79]	1985–1996		
Dyson[154]	1987–1996		
Castillo[81]	1987–1997		
Cheng[155]	1994–1999		AHA/ACC 1998[176]:

Di Filippo[156]	1966–2001	+ Real-time 3D first reports in 2001[43,44]	Mild: AVA > 1.5 cm^2 Moderate: AVA > 1.0–1.5 cm^2 Severe: AVA < 1.0 cm^2, mean ΔP > 50 mmHg
Castillo[93]	1987–2001		
Tariq[157]	1988–2001		
McKay[158]	1989–2001		
Tariq[159]	1997–2001		
Cecchi[160]	2000–2001		
Chu[96]	1997–2002		
Durante-Mangoni[161]	2000–2005	+ Speckle tracking (strain (2004))[45,46]	AHA/ACC 2006[5]: Mild: V_{max} < 3 m/s, ΔP < 25 mmHg, AVA > 1.5 cm^2 Moderate: V_{max} 3–4 m/s, mean ΔP 25–40 mmHg, AVA 1.0–1.5 cm^2
Assiri[162]	2002–2007		
Wong[113]	2002–2007		
Mokhles[115]	2001–2008		
Dzupova[118]	2007–2008		
Leone[122]	2004–2009		
Nakatani[163]	2007–2009		
Marks[164]	1998–2010		
Cecchi[165]	2007–2010		
Ma[166]	2002–2011		
Begezsan[167]	2007–2011		
Collins[168]	2008–2011		
Verheugt[141]	Before 2011		

Table 3 – Echocardiographic definitions of AS for the discussed literature

ΔP: mean pressure difference; 2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; AVA: aortic valve area; AVAI: aortic valve area index; CW: continuous wave; PW: pulsed wave TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography; V_{max}: maximum velocity

Definition of AS Today (AHA/ACC 2014[2])

At risk: V_{max} < 2 m/s

Mild: V_{max} 2.0–2.9 m/s or mean ΔP < 20 mmHg

Moderate: V_{max} 3.0–3.9 m/s or mean ΔP 2–9 mmHg

Severe: V_{max} ≥ 4 m/s or mean ΔP ≥ 40 mmHg, AVA < 1.0 cm^2 or AVAI ≤ 0.6 cm^2/m^2

Figure 13 – AS definition today

ΔP: pressure difference; AHA/ACC: American Heart Association/American College of Cardiology; AS: aortic valve stenosis; AVA: aortic valve area; AVAI: aortic valve area index; V_{max}: maximum velocity

7.4.1.4 Summary of Results

We identified only one study showing that a history of (congenital) AS was associated with a higher risk of IE, with a hazard ratio of 4.9.[141] No studies were identified for other causes of AS.

Forty-five studies were identified that published descriptive statistics on the proportion of patients with a history of AS in newly diagnosed IE cases. Of these studies, 11 (24.4%) included patients in the study only after the publication of the modified Duke criteria. A paired two-tailed t-test for the number of studies before and after 2001 was significant, with a p-value of 0.0003. The mean number of patients included in the 45 studies was 242 (median 106, IQR 62–212), in the studies prior to 2001 was 217 (median 98, IQR 63–179), and in the studies after 2001 was 322 (median 134, IQR 76–595). Of the 45 studies, the mean proportion of patients with a history of AS was 7.3% (median 6.7%, IQR 2.6%–9.7%). The distribution of these variables prior to 2001 was as follows: mean 8.0%, median 7.0%, IQR 2.5%–12.1%. After 2001, the numbers were as follows: mean 5.2%, median 4.5%, IQR 2.9%–7.1%. The difference between the two groups was not significant in an unpaired t-test. The dot plot that compares the study size with prevalence of prior IE in patients with IE and in association with IE in accordance with primary and modified Duke criteria shows a cluster consisting of studies with sample sizes below 200 patients and below 10% prevalence. However, the graph indicates that in larger and newer studies, the prevalence is most likely smaller than 5%.

The most important change concerning the echo criteria was the mean gradient, which defines the severity of AS. The guidelines from 2006 defined severe AS as having a mean gradient of ≥40 mmHg (instead of ≥50 mmHg in 1998), and the guidelines from 2014 changed the definition of moderate AS as beginning at ≥20 mmHg instead of ≥25 mmHg. Moreover, low-flow, low-gradient AS was defined first in 2006, which is important for patients with reduced systolic ejection fraction. Developments in

echo techniques and quality (e.g. better resolution of the screens, better transducers) also played an important role in improvements in diagnostics.

The differentiation between mild, moderate, and severe AS was described first in 1989.[173] Since 1998 – the year of the first publication of the ACC/AHA guidelines on valvular heart disease – the definition of mild, moderate, and severe AS has evolved. The observation that (i) three-quarters of the studies included patients prior to 2001, (ii) the mean and median proportions of patients with AS and IE were lower in studies published after 2001 (5.2% vs. 4.5%) than they were in studies published before 2001 (8% vs. 7%), and (iii) the dot plot demonstrates a prevalence of less than 5% in newer studies with large sample sizes indicates that the relevance of mild or moderate AS as a risk factor for IE is unknown. This corresponds to the study of Verheugt et al.[141] in that only congenital AS was statistically associated with a higher risk of developing IE. Gersony et al.[142] stated that only severe AS is related to the occurrence of IE.

In the preliminary meta-analysis, the proportion of patients with IE and AS as an underlying condition was 6.8% (95% CI 6.4%–7.4%) for a fixed effects model and 6.1% (95% CI 4.2%–8.3%) in a random effects model. One study contributed greatly to the overall heterogeneity.

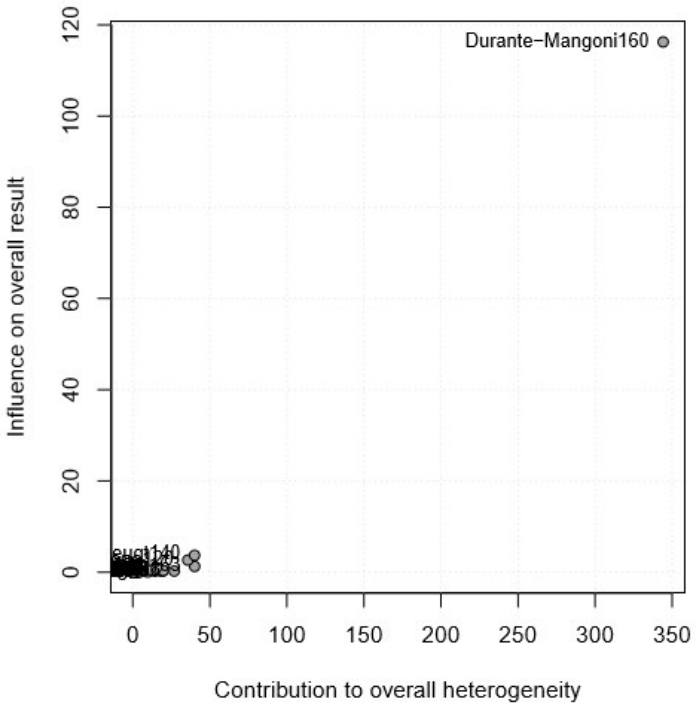

Figure 14 – Heterogeneity in meta-analysis for AS as an underlying condition for IE

AS: aortic valve stenosis; IE: infective endocarditis

7.4.2 Aortic Valve Insufficiency (AI)

Of the 207 articles considered relevant after the literature review, 39 mentioned AI.

7.4.2.1 Descriptive Statistics

Reference	Time	Place	Cases with (NV)IE	Cases (%) with AI	% with AI	Study Design
Falase[177]	1961–1970	Nigeria	90	9	10.0%	Retrospective, single centre
Bailey[178]	1962–1971	Australia	210	18	8.6%	Retrospective, single centre
Singham[179]	1968–1977	Malaysia	101	12	11.9%	Retrospective, single centre
Robbins[145]	1970–1977	USA	56	12	21.4%	Retrospective, single centre
Arbulu[180]	1968–1984	USA	417	36	26.0%	Retrospective, single centre
Hodes[148]	1977–1985	Ethiopia	51	1	2.0%	Retrospective, single centre
Blackett[181]	1984–1986	Cameroon	20	8	40.0%	Prospective, single centre
Mansur[149]	1978–1986	Brazil	287	15	5.2%	Retrospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	64	18.3%	Prospective epidemiologic study, multicentre
Agarwal[182]	1987–1988	India	28	1	3.6%	Single centre, probably prospective but not clearly stated
Iga[183]	1980–1989	Japan	32	4	12.5%	Retrospective, single centre
Nissen[66]	1980–1989	Denmark	132	5	3.8%	Retrospective, multicentre
Thamlikitkul[150]	1982–1989	Thailand	75	19	25.3%	Retrospective, single centre
Manford[184]	1983–1989	UK	33	1	3.0%	Retrospective, single centre
Strom[9]	1988–1990	USA	279	3	1.1%	Population-based, case-control study, multicentre
Choudhury[151]	1981–1991	India	186	15	8.1%	Retrospective, single centre
Delahaye[71]	1990–1991	France	415	27	6.5%	Prospective survey, multicentre
Benn[152]	1984–1993	Denmark	62	5	8.1%	Retrospective, multicentre

Sandre[75]	1985–1993	Canada	80	2	2.5%	Retrospective review, single centre
Werner[76]	1989–1993	Germany	106	6	5.7%	Retrospective, single centre
Netzer[153]	1980–1995	Switzerland	212	40	19.0%	Retrospective, single centre
Lamas[79]	1985–1996	UK	100	3	3.0%	Prospective, single centre
Castillo[81]	1987–1997	Spain	95	10	10.0%	Prospective case series, single centre
Khanal[185]	1995–1997	India	46	1	2.2%	Prospective observational, single centre
Castillo[93]	1987–2001	Spain	154	17	10.9%	Prospective observational, multicentre
McKay[158]	1989–2001	New Zealand	29	1	3.4%	Retrospective, multicentre
Garg[186]	1992–2001	India	192	8	4.2%	Retrospective, single centre
Tariq[159]	1997–2001	Pakistan	66	1	2.0%	Retrospective, single centre
Cecchi[160]	2000–2001	Italy	67	6	9.0%	Prospective, multicentre
Rehman[187]	2000–2001	Pakistan	30	1	3.3%	Prospective, single centre
Murdoch[105]	2005–2005	ICE cohort	2781	723	26.0%	Prospective cohort study, multicentre (ICE-PCS)
Assiri[162]	2002–2007	Saudi Arabia	44	14	31.8%	Retrospective, single centre
Dzupova[118]	2007–2008	Czech Republic	134	1	0.7%	Prospective, multicentre
Leone[122]	2004–2009	Italy	753	32	4.2%	Prospective, multicentre
Nakatani[163]	2007–2009	Japan	513	76	14.8%	Prospective survey, multicentre
Cecchi[165]	2007–2010	Italy	677	19	2.8%	Prospective, multicentre
Begezsan[167]	2007–2011	Romania	45	15	33.3%	Retrospective, single centre
Collins[168]	2008–2011	USA	95	1	1.1%	Prospective observational, single centre
Jain[188]	2011–2013	India	75	17	22.7%	Prospective observational, single centre

Table 4 – Literature for AI

AI: aortic valve insufficiency/regurgitation; ICE: International Collaboration on Endocarditis; ICE-PCS: International Collaboration on Endocarditis-Prospective Cohort Study; NVIE: native valve infective endocarditis

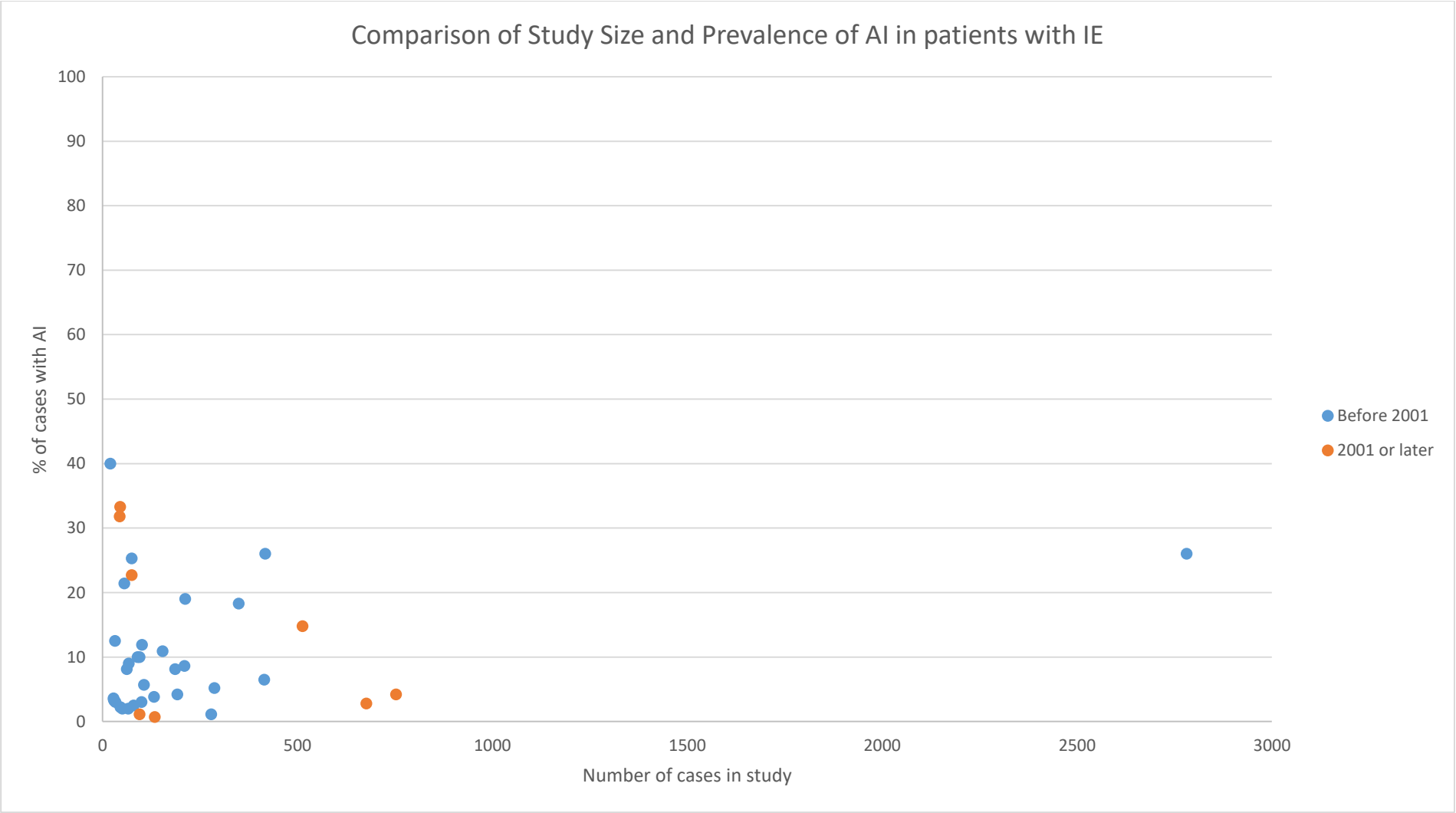

Figure 15 – Comparison of study size with prevalence of AI in patients with IE and in association with IE criteria prior to and after modified Duke criteria

AI: aortic valve insufficiency/regurgitation; IE: infective endocarditis

7.4.2.2 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Falase[177]	1961–1970	M-Mode (1954)[26]	
Bailey[178]	1962–1971		
Singham[179]	1968–1977	+ B-Mode (2D (1975))[34]	Danford et al. 1973[189]:
Robbins[145]	1970–1977		Severe: regurgitant flow (named QAr) 1.1–6.5 L/min
Arbulu [180]	1968–1984	+ Doppler (CW (1979[36,37]), PW (1982)),[40] TOE (1983)[41]	Bonow et al. 1983[190]:
Hodes[148]	1977–1985		Severe: visualisation by aortic root cineangiography (>3+)
Blackett[181]	1984–1986		
Mansur[149]	1978–1986		
Van der Meer[8]	1986–1988		Jaffe et al. 1988[191]:
Agarwal[182]	1987–1988		Severe: visualisation by aortic root cineangiography (≥3+), RF ≥ 30%
Iga[183]	1980–1989		
Nissen[66]	1980–1989		
Thamlikitkul[150]	1982–1989		
Manford[184]	1983–1989		
Strom[9]	1988–1990		
Choudhury[151]	1981–1991		
Delahaye[71]	1990–1991		
Benn[152]	1984–1993		
Sandre[75]	1985–1993		
Werner[76]	1989–1993		
Netzer[153]	1980–1995	+ TDI (1994)[174,175]	
Lamas[79]	1985–1996		
Castillo[81]	1987–1997		
Khanal[185]	1995–1997		
Castillo[93]	1987–2001	+ Real-time 3D first reports in 2001[43,44]	AHA/ACC 1998[176]
McKay[158]	1989–2001		Mild: not defined
Garg[186]	1992–2001		Moderate: not defined

Tariq[159]	1997–2001		Severe: Austin-Flint rumble, LV dilation (end-diastolic >70 mm, end-systolic >50 mm), reduced LV function, PHT < 300 ms
Cecchi[160]	2000–2001		
Rehman[187]	2000–2001		
Murdoch[105]	2005–2005	+ Speckle tracking (strain (2004))[45,46]	
Assiri[162]	2002–2007		AHA/ACC 2006[5] Mild: jet width < 25% of LVOT, VC < 0.3 cm, RVol < 30 ml/beat, RF < 30%, effective regurgitant orifice (ERO) < 0.10/m^2 Moderate: jet > mild, no severe AI, VC 0.3–0.6 cm, RVol 30–59 ml/beat, RF 30–49%, ERO 0.10–0.29/m^2 Severe: jet width > 65% of LVOT, VC > 0.6 cm, RVol ≥ 60 ml/beat, RF ≥ 50%, ERO ≥ 0.3/m^2
Dzupova[118]	2007–2008		
Leone[122]	2004–2009		
Nakatani[163]	2007–2009		
Cecchi[165]	2007–2010		
Begezsan[167]	2007–2011		
Collins[168]	2008–2011		
Jain[188]	2011–2013	3D echocardiography recommendations were published by EAE/ASE (2012)[47]	

Table 5 – Echocardiographic definitions of AI for the discussed literature

2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; AI: aortic valve insufficiency/regurgitation; CW: continuous wave; EAE/ASE: European Association of Echocardiography/American Society of Echocardiography; ERO: effective regurgitant orifice; LV: left ventricle; LVOT: left ventricular outflow tract; PHT: pressure half-time; PW: pulsed wave; RF: regurgitant fraction; RVol: regurgitant volume; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography; VC: vena contracta; V_{max}: maximum velocity

Definition of AI Today (AHA/ACC 2014[2])

Mild: jet width < 25% of LVOT, VC < 0.3 cm, RVol < 30 ml/beat, RF < 30%, ERO < 0.10/m^2

Moderate: jet 2%–4% of LVOT, VC 0.–.6 cm, RVol 3–9 ml/beat, RF 3%–9%, ERO 0.1–.29/m^2

Severe: jet width > 65% of LVOT, VC > 0.6 cm, RVol ≥ 60 ml/beat, RF ≥ 50%, ERO ≥ 0.3/m^2

Figure 16 – Definition of AI today

AI: insufficiency/regurgitation; AHA/ACC: American Heart Association/American College of Cardiology; ERO: effective regurgitant orifice; LVOT: left ventricular outflow tract; RF: regurgitant fraction; RVol: regurgitant volume; VC: vena contracta

7.4.2.3 Summary of Results

In our literature review, no studies with analytical statistics of patients with AI and their risk of developing IE could be identified.

Thirty-nine studies were identified that published descriptive statistics on the proportion of patients with a history of AI in newly diagnosed IE cases. Of these studies, eight (20.5%) included patients in the study after the publication of the modified Duke criteria. A paired two-tailed t-test for the number of studies published before and after 2001 was highly significant, with a p-value of <0.0001. The mean number of patients included in the 39 studies was 234 (median 95, IQR 53.5–211), in the studies prior to 2001 was 219 (median 95, IQR 53.5–201), and in the studies after 2001 was 292 (median 114.5, IQR 67.5–554). Of the 39 studies, the mean proportion of patients with a history of AI was 10.2% (median 8.1%, IQR 3.1%–16.55%). The distribution prior to 2001 was as follows: mean 10.2%, median 8.1%, IQR 3.3%–12.2%. After 2001, the numbers were as follows: mean 13.9%, median 9.5%, IQR 2.4%–25%. There was no statistical significance between proportions before and after 2001. The dot plot does not indicate a typical cluster, making the interpretation of these studies difficult.

Before 1998, visualisation by cineangiography and 'eyeball guessing' of the regurgitant volume was common. In 2003, with recommendations by the ASE,[192] and later in 2006 by implementations in the AHA guidelines,[5] the echo criteria were published. Since that time, the definition has not changed significantly. Eyeballing in transthoracic echocardiography is still common, but requires the skill of an experienced investigator and has not found its way into written definitions for the final diagnosis. Attention should be paid to inter-examiner variabilities in this context. Finally, finding the correct diagnosis almost always means using multimodal measurements and techniques (e.g. magnetic

resonance imaging [MRI], TOE). Thus, improvement in echo techniques contributed to the development of guidelines, and hence, the diagnosis of AI. Given the fact that 80% of publications addressed AI as a risk factor prior to the presentation of the modified Duke criteria, overestimation of AI as a predisposing condition is possible. The difficulty in assessing AI as a risk factor is reflected in the wide IQR of patients with AI and IE in publications after 2001 and the wide distribution in the dot plot graph that compares sample size and the prevalence of IE in patients with AI.

In the preliminary meta-analysis, the proportion of patients with IE and AI as an underlying condition was 11.7% (95% CI 11.1%–12.4%) for a fixed effects model and 8.8% (95% CI 5.9%–12.2%) in a random effects model. One study contributed greatly to the overall heterogeneity.

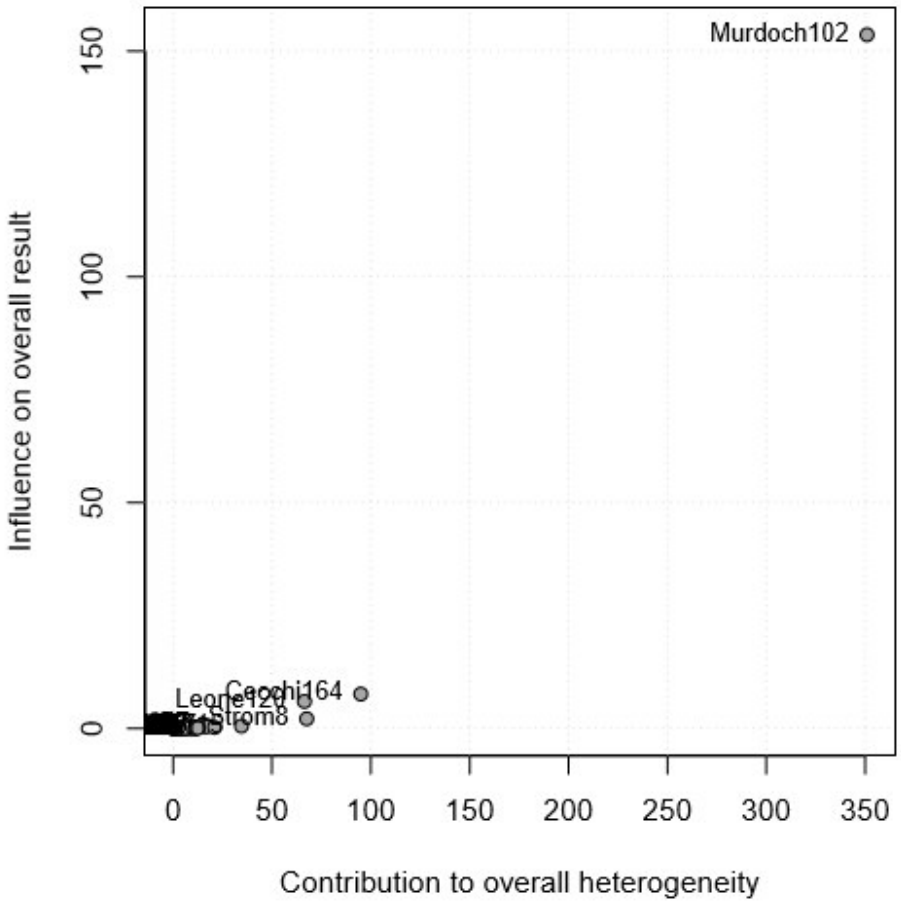

Figure 17 – Heterogeneity in meta-analysis for AI as an underlying condition for IE

AI: insufficiency/regurgitation; IE: infective endocarditis

7.4.3 Bicuspid Aortic Valve

Of the 207 articles considered relevant after the literature review, 78 mentioned BAV.

7.4.3.1 Analytical Statistics

Verheugt et al.[141] described patients from the CONCOR national registry for adults with congenital heart disease from the Netherlands. Of 551 patients with BAV, 31 (5.6%) developed IE. This correlates to a hazard ratio of 6.3 (95% CI 3.0–13.4).

7.4.3.2 Descriptive Statistics

Reference	Time	Place	Patients with (NV)IE	Cases (n) with BAV	Cases (%) with BAV	Study Design
Mills[193]	1950		41	3	7.3%	Prospective, single centre
Fenoglio[194]	1940–1970	USA	152	60	39.5%	Retrospective, single centre
Garvey[52]	1968–1973	USA	101	3	3.0%	Retrospective analysis of patient records, autopsy files, and files of the infectious diseases department
Thell[144]	1960–1974	USA	42	5	11.9%	Retrospective (pathology samples), multicentre
Welton[54]	1967–1976	USA	96	3	3.1%	Retrospective, single centre
Cassel[195]	1974–1976	South Africa	40	2	5.0%	Retrospective, single centre
Auger[196]	1969–1977	Canada	50	7	14.0%	Retrospective, single centre
Griffin[197]	1950–1981	USA	78	6	7.7%	Retrospective, multicentre
Rudolph[147]	Before 1983	Germany	50	4	8.0%	Single centre, probably prospective
Terpenning[59]	1976–1985	USA	154	6	3.9%	Retrospective review of patient charts, multicentre
Woo[198]	1971–1986	Hong Kong	176	1	0.6%	Mixed retrospective and prospective, single centre
Steckelberg[61]	1970–1987	USA	629	N/A	10%–12%	Retrospective from prospectively collected records, multicentre (comparison of a population- based cohort vs. cohort of Mayo Clinic)
Varstela[63]	1976–1987	Finland	58	29	50.0%	Retrospective, single centre
Cheng[199]	1979–1987	Taiwan	97	2	2.1%	Retrospective, single centre
Borger[200]	1979–1993	Canada	201	12	6.0%	Retrospective, single centre

Hogevik[65]	1984–1988	Sweden	98	7	7.0%	Prospective non-randomised, single centre
Kiwan[201]	1985–1988	Kuwait	60	3	5.0%	Prospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	5	1.4%	Prospective epidemiologic study, multicentre
Agarwal[182]	1987–1988	India	28	3	10.7%	Single centre, probably prospective, but not clearly stated
Strom[9]	1988–1990	USA	279	5	1.8%	Population-based, case-control study, multicentre
Choudhury[151]	1981–1991	India	186	25	13.4%	Retrospective, single centre
Delahaye[71]	1990–1991	France	415	2	0.5%	Prospective survey, multicentre
Vlessis[202]	1982–1992	USA	194	10	5.0%	Retrospective, single centre
Rognon[74]	1983–1993	Switzerland	179	12	6.7%	Retrospective, multicentre
Sandre[75]	1985–1993	Canada	80	12	15.0%	Retrospective review, single centre
Lamas[79]	1985–1996	UK	100	26	26.0%	Prospective, single centre
Dyson[154]	1987–1996	UK	78	13	16.7%	Retrospective, single centre
Jalal[203]	1982–1997	India	466	55	11.8%	Retrospective, single centre
Lamas[204]	1970–1998	UK	408	50	12.3%	Retrospective, single centre
Michelena[205]	1980–1999	USA	212	4	1.9%	Prospective, multicentre
Michelena[206,207]	1980–1999	USA	486	9	1.9%	Retrospective cohort study, multicentre
Tleyjeh[87]	1970–2000	USA	107	8	7.0%	Retrospective (population-based survey), multicentre
Alestig[89]	1984–2000	Sweden	98	7	7.0%	Prospective clinical studies carried out in Göteborg since 1984, data obtained from a Swedish national registry of IE since 1995 and existing literature
Tran[208]	1998–2000	Denmark	132	10	7.6%	Retrospective, single centre

Di Filippo[156]	1966–2001	France	153	4	2.6%	Retrospective, single centre
Tariq[157]	1988–2001	Pakistan	159	4	2.5%	Retrospective, single centre
McKay[158]	1989–2001	New Zealand	29	7	24.1%	Retrospective, multicentre
Garg[186]	1992–2001	India	192	18	9.3%	Retrospective, single centre
Tzemos[209]	1994–2001	Canada	642	13	2.0%	Retrospective, single centre
Tariq[159]	1997–2001	Pakistan	66	2	3.0%	Retrospective, single centre
Cecchi[160]	2000–2001	Italy	67	8	11.9%	Prospective, multicentre
Chu[96]	1997–2002	New Zealand	65	5	7.7%	Retrospective, single centre
Ferreiros[77]	2001–2002	Argentina	390	10	2.6%	Prospective, multicentre
Nashmi[99]	1993–2003	Saudi Arabia	47	1	2.1%	Retrospective, single centre
Hsu[100]	1995–2003	Taiwan	315	4	1.3%	Retrospective review, single centre
Heiro[210,211]	1980–2004	Finland	326	38	11.7%	Retrospective, single centre
Hill[102]	2000–2004	Belgium	203	11	5.0%	Prospective observational cohort study, single centre
Suzuki[212]	1988–2005	Japan	27	1	3.7%	Retrospective, single centre
Collins[213]	2002–2005	Canada	327	5	1.5%	Retrospective, single centre
Correa de Sa[107]	1970–2006	USA	150	8	5.3%	Retrospective, multicentre
Pazdernik[109]	1998–2006	Czech Republic	106	14	13.2%	Retrospective, single centre
Kahveci[214]	2002–2006	Turkey	51	22	43.0%	Retrospective, single centre
Mokhles[115]	2001–2008	Netherlands	191	8	4.2%	Retrospective observational cohort study, single centre
Erbay[117]	2004–2008	Turkey	107	3	2.8%	Retrospective, single centre
Dzupova[118]	2007–2008	Czech Republic	134	7	5.2%	Prospective, multicentre
Li[215]	1998–2009	China	220	40	18.2%	Retrospective, single centre
Fernandez-Hidalgo[121]	2000–2009	Spain	337	19	5.6%	Prospective observational cohort study, single centre
Tribouilloy[216]	2005–2009	France	148	4	2.7%	Prospective, observational, multicentre
Tribouilloy[216]	2005–2009	France	310	50	16.2%	Prospective, observational, multicentre

Nakatani[163]	2007–2009	Japan	513	24	4.7%	Prospective survey, multicentre
Lu[217]	1998–2010	Australia	148	18	12.0%	Retrospective observational study, single centre
Marks[164]	1998–2010	UK	336	36	10.7%	Retrospective observational cohort study, single centre
Gupta[128]	2005–2010	India	83	10	16.4%	Retrospective, single centre
Senthilkumar[218]	2008–2010	India	116	5	4.3%	Prospective, single centre
Sadaka[219]	2009–2010	Egypt	50	1	2.0%	Prospective, single centre
Ma[166]	2002–2011	China	115	9	7.8%	Single centre
Collins[168]	2008–2011	USA	95	18	19.0%	Prospective observational, single centre
Collins[168]	2008–2011	USA	95	11	11.6%	Prospective observational, single centre
Turak[135]	2009–2011	Turkey	122	4	3.0%	Retrospective, single centre
Verheugt[141]	Before 2011	Netherlands	551	31	5.6%	Prospective cohort study, multicentre
Baek[220]	1987–2012	South Korea	325	1	0.3%	Retrospective, single centre
Elbey[221]	2005–2012	Turkey	158	5	3.2%	Retrospective, multicentre
Simsek-Yavuz[138]	2000–2013	Turkey	325	18	5.5%	Prospective 102 (first 5 years) and retrospective 223 thereafter, single centre
Gupta[140]	2010–2013	India	109	11	10.1%	Retrospective, single centre
Jain[188]	2011–2013	India	75	4	5.3%	Prospective observational, single centre

Table 6 – Literature for BAV: Patients with IE with BAV as an underlying condition

BAV: bicuspid aortic valve; IE: infective endocarditis; N/A: not available; NVIE: native valve infective endocarditis

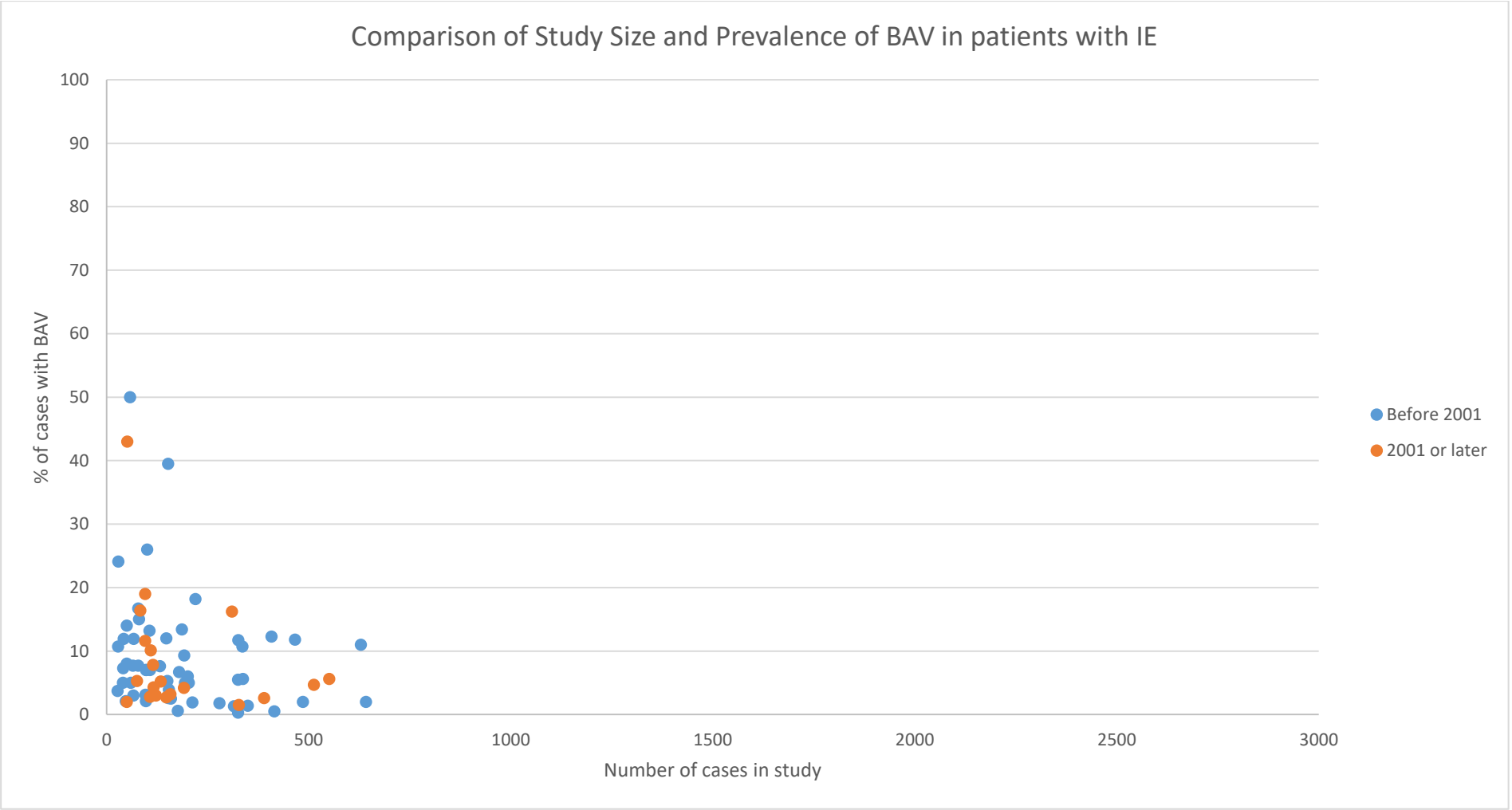

Figure 18 – Comparison of study size with prevalence of BAV in patients with IE and in association with IE criteria prior to and after modified Duke criteria

BAV: bicuspid aortic valve; IE: infective endocarditis

7.4.3.3 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition Then
Fenoglio[194]	1940–1970	M-Mode (1954)[26]	
Garvey[52]	1968–1973		
Thell[144]	1960–1974		
Welton[54]	1967–1976	+ B-Mode (2D (1975))[34]	
Cassel[195]	1974–1976		
Auger[196]	1969–1977		
Griffin[197]	1950–1981	+ Doppler (CW (1979))[36,37]	
Rudolph[147]	Before 1983	+ PW (1982)[40]	
Terpenning[59]	1976–1985	+ TOE (1983)[41]	
Woo[198]	1971–1986		
Steckelberg[61]	1970–1987		
Varstela[63]	1976–1987		
Cheng[199]	1979–1987		
Hogevik[65]	1984–1988		
Kiwan[201]	1985–1988		
Van der Meer[8]	1986–1988		
Agarwal[182]	1987–1988		
Strom[9]	1988–1990		
Choudhury[151]	1981–1991		
Delahaye[71]	1990–1991		
Vlessis[202]	1982–1992		
Borger[200]	1979–1993		
Rognon[74]	1983–1993		
Sandre[75]	1985–1993		
Lamas[79]	1985–1996	+ TDI (1994)[174,175]	
Dyson[154]	1987–1996		
Jalal[203]	1982–1997		

Lamas[204]	1970–1998		
Michelena[205]	1980–1999		
Michelena[206,207]	1980–1999		
Tleyjeh[87]	1970–2000		
Alestig[89]	1984–2000		
Tran[208]	1998–2000		
Di Filippo[156]	1966–2001	+ Real-time 3D first reports in 2001[43,44]	
Tariq[157]	1988–2001		
McKay[158]	1989–2001		
Garg[186]	1992–2001		
Tzemos[209]	1994–2001		
Tariq[159]	1997–2001		
Cecchi[160]	2000–2001		
Chu[96]	1997–2002		
Ferreiros[77]	2001–2002		
Nashmi[99]	1993–2003		
Hsu[100]	1995–2003		
Heiro[210,211]	1980–2004	+ Speckle tracking (strain (2004))[45,46]	
Hill[102]	2000–2004		
Suzuki[212]	1988–2005		
Collins[213]	2002–2005		
Correa de Sa[107]	1970–2006		
Pazdernik[109]	1998–2006		
Mokhles[115]	2001–2008		
Erbay[117]	2004–2008		
Dzupova[118]	2007–2008		
Li[215]	1998–2009		
Fernandez-Hidalgo[121]	2000–2009		
Tribouilloy[216]	2005–2009		
Nakatani[163]	2007–2009		
Lu[217]	1998–2010		

Marks[164]	1998–2010		
Gupta[128]	2005–2010		
Senthilkumar[218]	2008–2010		
Sadaka[219]	2009–2010		
Ma[166]	2002–2011		
Collins[168]	2008–2011		
Turak[135]	2009–2011		
Verheugt[141]	Before 2011		
Baek[220]	1987–2012	+ 3D echocardiography recommendations were published by EAE/ASE (2012)[47]	
Elbey[221]	2005–2012		
Simsek-Yavuz[138]	2000–2013		
Gupta[140]	2010–2013		
Jain[188]	2011–2013		

Table 7 – Echocardiographic criteria for BAV for the discussed literature

2D: two-dimensional; 3D: three-dimensional; CW: continuous wave; EAE/ASE: European Association of Echocardiography/American Society of Echocardiography; PW: pulsed wave; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography

Definition of BAV Today: (AHA/ACC 2014[2])

Fusion of aortic valve cusps in different positions

Figure 19 – Definition of BAV today

AHA/ACC: American Heart Association/American College of Cardiology; BAV: bicuspid aortic valve

7.4.3.4 Summary of Results

We identified one study showing that a history of BAV was associated with a higher risk of IE, with a hazard ratio of 6.3.[141]

Seventy-seven studies were identified that published descriptive statistics on the proportion of patients with a history of BAV in newly diagnosed IE cases. Of these studies, 20 (26%) included patients in the study after the publication of the modified Duke criteria. A paired two-tailed t-test of the number of studies published before and after 2001 was highly significant, with a p-value of <0.0001. The mean number of patients included in the 77 studies was 185 (median 134, IQR 79–249.5), in the studies prior to 2001 was 185 (median 150, IQR 72.5–249.5), and in the studies after 2001 was 187 (median 119, IQR 95–221). Of the 77 studies, the mean proportion of patients with a history of previous IE was 8.8% (median 5.6%, IQR 3%–12%). The distribution prior to 2001 was as follows: mean 8.9%, median 7.0%, IQR 3%–12%. After 2001, the numbers were as follows: mean 8.6%, median 5.0%, IQR 3%–10%. The differences between groups were not significant in an unpaired t-test. The dot plot graph that compares the prevalence of IE in patients with BAV and the sample size in each study indicates a pattern with a publication bias of less than 30% among the included studies. The majority of studies, including those with large sample sizes, indicate a median prevalence of approximately 5%.

BAV is visually detectable by fluoroscopy, but with the introduction of echocardiography, whose use was first published in 1974 by Nanda et al.,[222] it was possible to more easily and more quickly make a diagnosis in a non-invasive manner. In 1974, the authors used M-Mode echocardiography, which is not the standard technique today. Consequently, the improvements in echo technique by means of 2D or 3D echocardiography, TOE, better transducers, and high-definition screens has surely influenced the presence or absence of BAV in the reviewed studies. Imaging techniques such as MRI and computed tomography-angiography play another important role today. Nonetheless, there are no obvious indications that the improvement in technique influenced the presence or absence of BAV in the reviewed studies.

In the preliminary meta-analysis, the proportion of patients with IE and BAV as an underlying condition was 5.8% (95% CI 5.4%–6.2%) for a fixed effects model and 7.1% (95% CI 5.7%–8.7%) in a random effects model. As a few studies contributed greatly to the overall heterogeneity, a second meta-analysis with stricter clinical inclusion/exclusion criteria is planned.

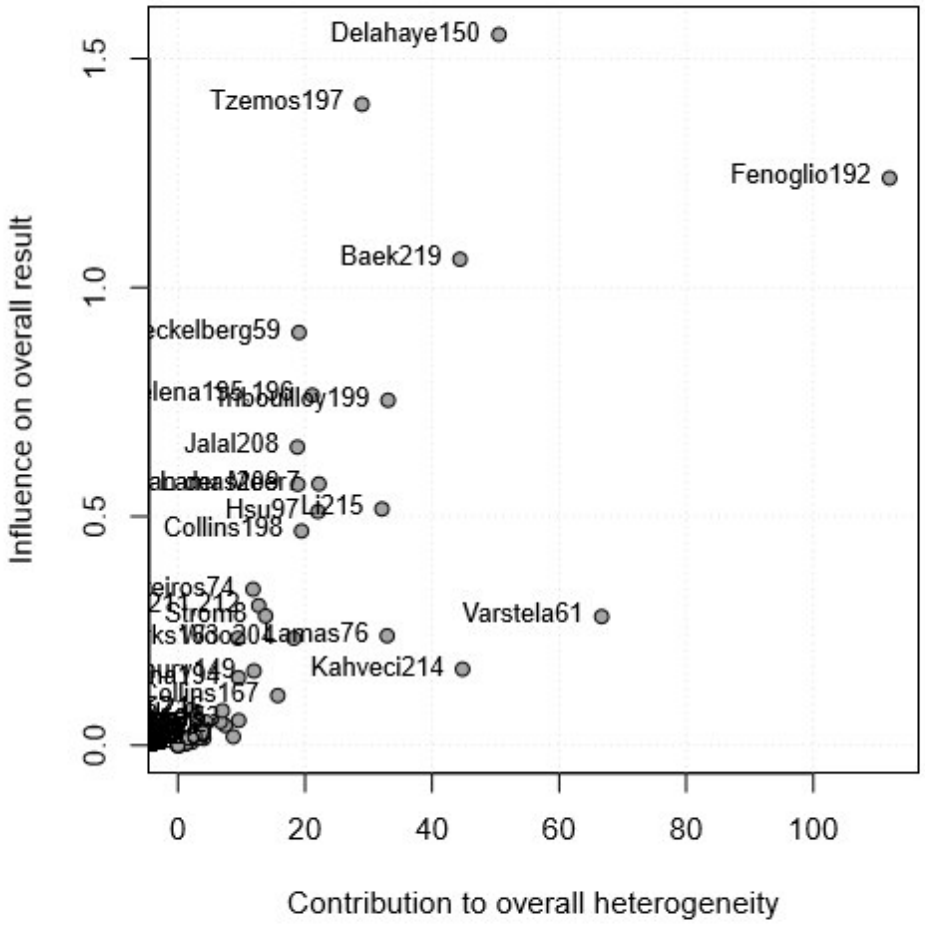

Figure 20 – Heterogeneity in meta-analysis for BAV as an underlying condition for IE

BAV: bicuspid aortic valve; IE: infective endocarditis

7.5 Mitral Valve

7.5.1 Mitral Valve Prolapse (MVP)

Of the 207 articles considered relevant after the literature review, 111 mentioned MVP.

7.5.1.1 Analytical Statistics

Clemens et al. presented 51 patients with IE from Yale-New Haven Hospital (USA) from 1976 to 1980. In a case-control study with 153 matched controls without IE, 25% of patients had MVP compared with 10% of the controls. The odds ratio for developing IE with MVP was 8.2, indicating a substantially higher risk of IE for people with MVP than for people without it.[20]

Devereux et al.[223] described 31 patients with MI from 1980 to 1983 and 67 patients with native valve IE from 1978 to 1982 from the USA. In addition, they reported 81 consecutive relatives with MVP, 196 population controls, and 2146 clinical controls. They described the odds ratio for developing IE with MVP as 4.6 to 4.8 (depending on the control group). With a matched-triplets analysis, the odds ratio was 6.7 (95% CI 1.96–22.9).

MacMahon et al.[224] reported 19 patients with IE and MVP from Australia between 1976 and 1984, as well as 57 control subjects with MVP. They reported that the relative risk of IE associated with the presence of a systolic murmur in a patient with MVP was 13.0 (95% CI 2.1–79.0). The absolute risk of developing IE in a patient with MVP and a systolic murmur was 0.0007 per year (95% CI 0.0004–0.0014). The lifetime risk of IE in a patient with MVP and a murmur increased by 1% every 15 years. The absolute risk of IE occurring in a patient with MVP without murmur was estimated to be 0.00002 per year.

Danchin et al.[225] reported 48 cases of mitral valve IE from 1981 to 1986 from CHU Nancy-Brabois (France). Nine (19%) of the patients with mitral valve IE had MVP. Six (6%) of 96 controls had MVP. For this reason, the authors stated that the risk of developing IE was three times higher in patients with MVP than without MVP. The risk was 14 times higher for patients with MVP and a systolic murmur, and there was no increased risk for patients with MVP without a murmur. In patients without rheumatic heart disease, the risk of developing IE was increased by 27 times for patients with MVP and a murmur compared with healthy controls, and it was increased by six times in patients with MVP and no murmur.

Strom et al.[9] reviewed 279 cases of IE from 1988 to 1990 from 54 hospitals in Delaware Valley (USA). Compared with that in the controls, the odds ratio of developing IE with MVP was 19.2.

Zuppiroli et al.[226] reported 275 patients with MVP from 1979 to 1996 from Italy with a mean follow-up of 98 months, with a total of 2245 patient-years. One patient developed IE, which resulted in a rate of 1/2500 patient-years. The authors stated that the risk of IE among MVP patients was about 8 times that in the general population, but the risk in their study was relatively low compared with other reports.

7.5.1.2 Descriptive Statistics

Reference	Time	Place	Patients with (NV)IE	Cases with MVP	% with MVP	Study Design
Mills[227]	1950s and 1960s		53	3	5.7%	Retrospective, single centre
Thell[144]	1960–1974	USA	42	2	4.8%	Retrospective (pathology samples), multicentre
Lowes[53]	1966–1975	UK	60	3	5.0%	Retrospective survey, single centre
Corrigall[228]	1969–1975	USA	87	10	11.5%	Retrospective, single centre
Cassel[195]	1974–1976	South Africa	40	5	12.5%	Retrospective, single centre
Grossman[146]	1951–1979	Israel	228	5	2.2%	Retrospective, single centre
Nishimura[229]	1975–1979	USA	237	3	1.3%	Prospective, single centre
Tresch[230]	Before 1979		40	4	10.0%	Single centre
Hammel[56]	1971–1980	Switzerland	31	7	22.6%	Single centre, not indicated whether prospective or retrospective
Venezio[57]	1972–1980	USA	32	3	9.4%	Retrospective, single centre
Griffin[197]	1950–1981	USA	78	13	17.0%	Retrospective, multicentre
Roucaut[231]	1970–1982	France	350	14	4.0%	Retrospective, single centre
Beton[21]	Before 1983	UK	182	8	4.4%	Prospective, single centre
Rudolph[147]	Before 1983	Germany	50	10	20.0%	Single centre, probably prospective
Duren[232]	1963–1983	Netherlands	300	24	8.0%	Prospective, single centre
Devereux[223]	1980–1983	USA	67	11	16.4%	Case-control study, single centre
MacMahon[224]	1976–1984	Australia	136	19	14.0%	Prospective matched case-control study, multicentre
Skehan[233]	1982–1984	UK	198	38	19.0%	Prospective, multicentre
Terpenning[59]	1976–1985	USA	154	14	9.1%	Retrospective review of patient charts, multicentre
Vered[234]	Before 1985	Israel	42	5	11.9%	Retrospective, single centre
Naggar[235]	Before 1986	USA	145	7	4.8%	Retrospective, single centre
Peat[236]	1976–1986	New Zealand	78	5	6.4%	Retrospective, single centre

Mansur[149]	1978–1986	Brazil	287	26	9.1%	Retrospective, single centre
Wells[237]	1979–1986	New Zealand	102	11	10.8%	Retrospective, single centre
Zuppiroli[226]	1979–1986	Italy	316	2	0.6%	Prospective observational, single centre
Danchin[225]	1981–1986	France	102	9	8.8%	Retrospective case-control study, single centre
Marks[238]	1982–1986	USA	456	11	2.4%	Retrospective, single centre
Steckelberg[61]	1970–1987	USA	697	N/A	15-17%	Retrospective from prospectively collected records, multicentre (comparison of a population- based cohort vs. cohort of Mayo Clinic)
Weinberger[23]	1970–1987	Israel	135	19	14.0%	Retrospective, single centre
Cheng[199]	1979–1987	Taiwan	97	11	11.3%	Retrospective, single centre
Manford[184]	1983–1987	UK	33	1	3.0%	Retrospective, single centre
Hogevik[65]	1984–1988	Sweden	98	7	7.0%	Prospective non-randomised, single centre
Kiwan[201]	1985–1988	Kuwait	60	5	8.3%	Prospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	29	8.3%	Prospective epidemiologic study, multicentre
Nissen[66]	1980–1989	Denmark	132	0	0.0%	Retrospective, multicentre
Thamlikitkul[150]	1982–1989	Thailand	75	5	6.7%	Retrospective, single centre
Schon[67]	1980–1989	Germany	51	6	11.8%	Retrospective, single centre
Watanakunakorn[69]	1980–1990	USA	181	12	6.6%	Retrospective 1980–1985, prospective 1986–1990, single centre
Strom[9]	1988–1990	USA	279	52	18.6%	Population-based, case-control study, multicentre
Choudhury[151]	1981–1991	India	186	2	1.1%	Retrospective, single centre
Delahaye[71]	1990–1991	France	415	13	3.1%	Prospective survey, multicentre
Tornos[73]	1975–1992	Spain	194	20	10.3%	Prospective observational, single centre
Vlessis[202]	1982–1992	USA	194	22	11.4%	Retrospective, single centre
Benn[152]	1984–1993	Denmark	62	1	1.6%	Retrospective, multicentre
Sandre[75]	1985–1993	Canada	80	10	13.0%	Retrospective review, single centre

Kim[239]	1986–1993	Japan	229	1	0.4%	Prospective, single centre
Werner[76]	1989–1993	Germany	106	7	6.6%	Retrospective, single centre
Siddiq[240]	1990–1993	USA	159	5	3.1%	Prospective, single centre
Yeo[241]	1991–1993	Singapore	98	5	5.1%	Retrospective, single centre
Ferreiros[77]	1992–1993	Argentina	294	28	9.5%	Prospective registry, multicentre
Borer[242]	1980–1994	Israel	71	7	9.9%	Retrospective, single centre
Weng[78]	1984–1994	Taiwan	109	9	8.3%	Retrospective, single centre
Netzer[153]	1980–1995	Switzerland	212	11	5.0%	Retrospective, single centre
Zuppiroli[226]	1979–1996	Italy	275	1	0.4%	Prospective observational, single centre
Lamas [79]	1985–1996	UK	100	6	6.0%	Prospective, single centre
Dyson[154]	1987–1996	UK	78	9	11.5%	Retrospective, single centre
Bouza[80]	1994–1996	Spain	109	1	0.9%	Prospective observational case series, single centre
Jalal[203]	1982–1997	India	466	4	0.9%	Retrospective, single centre
Castillo[81]	1987–1997	Spain	95	8	8.0%	Prospective case series, single centre
Khanal[185]	1995–1997	India	46	2	4.3%	Prospective observational, single centre
Cetinkaya[84]	1974–1999	Turkey	228	5	2.2%	Retrospective (hospital charts) review, single centre
Ako[243]	1980–1999	Japan	194	13	6.7%	Single centre, retrospective (admission records)
Fefer[85]	1990–1999	Israel	108	9	12.0%	Retrospective (medical records), single centre
Hoen[244]	1999	France	390	35	9.0%	Retrospective population based survey, multicentre
Tleyjeh[87]	1970–2000	USA	107	18	17.0%	Retrospective (population-based survey), multicentre
Alestig [89]	1984–2000	Sweden	98	7	7.0%	Prospective clinical studies carried out in Göteborg since 1984, data obtained from a Swedish national registry of IE since 1995 and existing literature

Koegelenberg[91,92]	1997–2000	South Africa	47	1	2.1%	Prospective observational study, single centre
Loupa[245]	1997–2000	Greece	101	2	2.0%	Prospective, multicentre
Di Filippo[156]	1966–2001	France	153	4	2.6%	Retrospective, single centre
Castillo[93]	1987–2001	Spain	154	20	12.7%	Prospective observational, multicentre
Tariq[157]	1988- 2001	Pakistan	159	10	6.3%	Retrospective, single centre
McKay[158]	1989–2001	New Zealand	29	3	10.3%	Retrospective, multicentre
Garg[186]	1992–2001	India	192	6	3.1%	Retrospective, single centre
Tariq[159]	1997–2001	Pakistan	66	5	8.0%	Retrospective, single centre
Cecchi[160]	2000–2001	Italy	67	25	37.3%	Prospective, multicentre
Rehman[187]	2000–2001	Pakistan	30	3	10.0%	Prospective, single centre
Chu[96]	1997–2002	New Zealand	65	4	6.1%	Retrospective, single centre
Yousuf[97]	2000–2002	Malaysia	45	2	4.4%	Retrospective analysis of case records, single centre
Ferreiros[77]	2001–2002	Argentina	390	36	9.2%	Prospective, multicentre
Heiro[210,211]	1980–2004	Finland	326	33	10.1%	Retrospective, single centre
Hill[102]	2000–2004	Belgium	203	19	9.0%	Prospective observational cohort study, single centre
Yiu[246]	1995–2005	Hong Kong	172	14	8.1%	Retrospective cohort, single centre
Correa de Sa[107]	1970–2006	USA	150	25	16.7%	Retrospective, multicentre
Knudsen[247]	2000–2006	Denmark	172	5	2.9%	Prospective, single centre
Math[248]	2004–2006	India	104	3	2.9%	Prospective observational study, single centre
Tugcu[110]	1997–2007	Turkey	28	2	7.1%	Retrospective review, single centre
Assiri[162]	2002–2007	Saudi Arabia	44	2	4.5%	Retrospective, single centre
Wong[113]	2002–2007	New Zealand	57	8	14.0%	Retrospective review, single centre
Scudeller[249]	2004–2008	Italy	254	27	10.6%	Prospective observational, multicentre
Castillo[250]	1987–2009	Spain	228	30	13.0%	Prospective, single centre
Nakagawa[251]	1990–2009	Japan	112	10	8.9%	Retrospective, single centre
Li[215]	1998–2009	China	220	40	18.2%	Retrospective, single centre
Sun[252]	2000–2009	South Korea	328	82	25.0%	Retrospective, single centre

Nakatani[163]	2007–2009	Japan	513	55	10.7%	Prospective survey, multicentre
Hajihossainlou[253]	1995–2010	Iran	286	71	24.8%	Retrospective, multicentre
Lu[217]	1998–2010	Australia	148	7	5.0%	Retrospective observational study, single centre
Poesen[127]	2003–2010	Belgium	88	1	1.1%	Retrospective, single centre
Gupta[128]	2005–2010	India	83	2	3.3%	Retrospective, single centre
Cecchi[165]	2007–2010	Italy	677	45	6.7%	Prospective, multicentre
Senthilkumar[218]	2008–2010	India	116	7	6.0%	Prospective, single centre
Sadaka[219]	2009–2010	Egypt	50	1	2.0%	Prospective, single centre
Ma[166]	2002–2011	China	115	12	10.4%	Single centre
Al Abri[254]	2006–2011	Oman	48	8	13.8%	Single centre, retrospective (computerised activity register)
Collins[168]	2008–2011	USA	N/A	N/A	7.0%	Prospective observational, single centre
Collins[168]	2008–2011	USA	95	5	5.3%	Prospective observational, single centre
Turak[135]	2009–2011	Turkey	122	5	4.0%	Retrospective, single centre
Elbey[221]	2005–2012	Turkey	158	9	5.7%	Retrospective, multicentre
Watt[255]	2010–2012	Thailand	132	19	14.4%	Prospective observational, multicentre
Gupta[140]	2010–2013	India	109	8	7.3%	Retrospective, single centre
Jain[188]	2011–2013	India	75	5	6.7%	Prospective observational, single centre

Table 8 – Literature for MVP: Patients with IE with MVP as an underlying condition

IE: infective endocarditis; MVP: mitral valve prolapse; N/A: not available; NVIE: native valve infective endocarditis

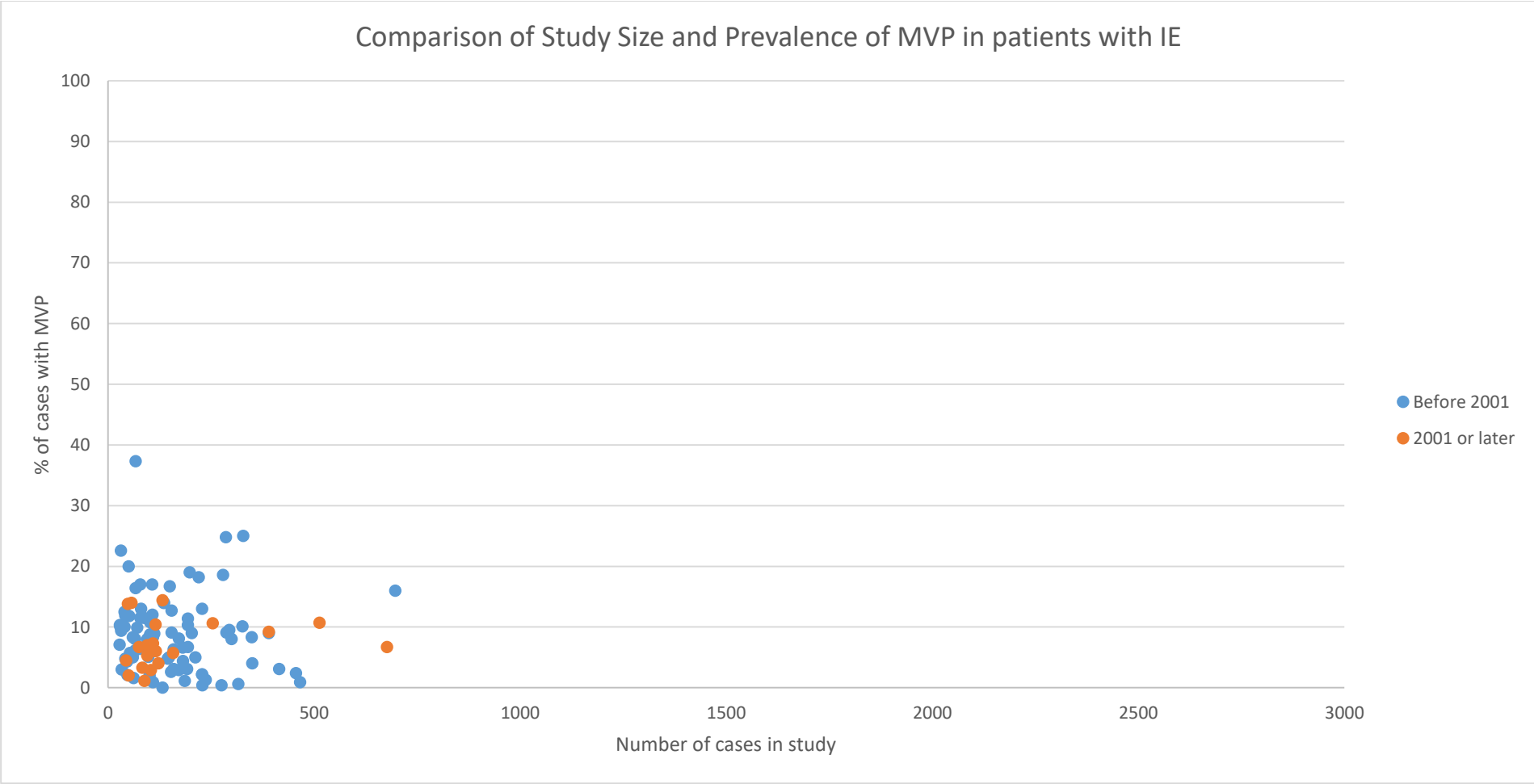

Figure 21 – Comparison of study size with prevalence of MVP in patients with IE and in association with IE criteria prior to and after modified Duke criteria

IE: infective endocarditis; MVP: mitral valve prolapse

7.5.1.3 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Mills[227]	1950s and 1960s	M-Mode (1954)[26]	Barlow et al. (1966, 1968)[256,257]: Clinical: mid- to late systolic click Pathological: - excessive myxomatous tissue - annular dilatation - leaflet thickening - bileaflet prolapse - chordal lengthening - frequently, valvular tissue calcification Engle et al. (1969)[258]: ECG: abnormal T-waves and late systolic click Popp et al. (1974)[259]: Echo: during systole the normal pattern of gradual anterior migration of the closed mitral leaflets is replaced by the pattern of an initial horizontal, slight anterior, or posterior motion, followed by an abrupt posterior motion
Thell[144]	1960–1974		
Lowes[53]	1966–1975	+ B-Mode (2D (1975))[34]	Weiss et al. (1975)[260]: Echo: mid-systolic buckling and pansystolic hammock-like posterior motion of the valve leaflets Devereux et al. (1976)[261]: Echo: late systolic prolapse of one or both leaflets can be directly visualised by echocardiography as posterior movement interrupting the normal anterior motion Nishimura et al. (1985, years including 1975-1979)[229]: Echo (M-Mode): - 3 mm or more below the C-D line (line of coaptation) - leaflet thickness ≥5 mm
Corrigall[228]	1969–1975		
Cassel[195]	1974–1976		
Grossman[146]	1951–1979	+ Doppler (CW (1979))[36,37]	
Nishimura[229]	1975–1979		
Tresch[230]	Before 1979		
Hammel[56]	1971–1980		
Venezio[57]	1972–1980		
Griffin[197]	1950–1981		
Roucaut[231]	1970–1982	+ PW (1982)[40]	
Rudolph[147]	Before 1983		
Beton[21]	Before 1983		

Duren[232]	1963–1983		
Devereux[223]	1980–1983	+ TOE (1983)[41]	
MacMahon[224]	1976–1984		
Skehan[233]	1982–1984		
Vered[234]	Before 1985		
Terpenning[59]	1976–1985		
Peat[236]	1976–1986		
Mansur[149]	1978–1986		
Wells[237]	1979–1986		
Zuppiroli[226]	1979–1986		
Danchin[225]	1981–1986		
Marks[238]	1982–1986		
Naggar[235]	Before 1986		
Steckelberg[61]	1970–1987		Barron et al. (1987/1988)[262]: Echo: MVP was diagnosed by systolic motion of either or both mitral valve leaflets beyond the plane of the mitral ring into the left atrium in both the parasternal long-axis and apical four-chamber views (at least 1–2 mm)
Weinberger[23]	1970–1987		
Cheng[199]	1979–1987		
Manford[184]	1983–1987		
Hogevik[65]	1984–1988		
Kiwan[201]	1985–1988		
Van der Meer[8]	1986–1988		
Nissen[66]	1980–1989		
Thamlikitkul[150]	1982–1989		
Schon[67]	1980–1989		
Watanakunakorn[69]	1980–1990		
Strom[9]	1988–1990		
Choudhury[151]	1981–1991		
Delahaye[71]	1990–1991		
Tornos[73]	1975–1992		
Vlessis[202]	1982–1992		
Benn[152]	1984–1993		
Sandre[75]	1985–1993		
Kim[239]	1986–1993		

Werner[76]	1989–1993		
Siddiq[240]	1990–1993		
Ferreiros[77]	1992–1993		
Borer[242]	1980–1994	+ TDI (1994)[174,175]	
Weng[78]	1984–1994		
Netzer[153]	1980–1995		
Zuppiroli[226]	1979–1996		
Lamas [79]	1985–1996		
Dyson[154]	1987–1996		
Bouza[80]	1994–1996		
Jalal[203]	1982–1997		
Castillo[81]	1987–1997		
Khanal[185]	1995–1997		
Cetinkaya[84]	1974–1999		AHA/ACC 1998[176]:
Ako[243]	1980–1999		Clinical: midsystolic click, frequently followed by a late systolic murmur
Fefer[85]	1990–1999		ECG:
Yeo[241]	1991–1993		- often normal
Hoen[244]	1999		- non-specific ST-T wave changes, T-wave inversion, prominent U waves, and QT prolongation can occur
Tleyjeh[87]	1970–2000		Echo:
Alestig [89]	1984–2000		- no consensus on the 2D echocardiographic criteria for MVP
Koegelenberg[91,92]	1997–2000		- M-Mode echo definition of MVP includes ≥2 mm posterior displacement of one or both leaflets or holosystolic posterior 'ham-mocking' ≥3 mm
Loupa[245]	1997–2000		- 2D echo: high likelihood of MVP if systolic displacement of one or both mitral leaflets in the parasternal long-axis view, particularly when they coapt on the atrial side of the annular plane
Di Filippo[156]	1966–2001	+ Real-time 3D first reports in 2001[43,44]	- MVP is more certain when leaflet thickness is >5 mm
Castillo[93]	1987–2001		- on Doppler MVP is more likely when MR is detected as a high-velocity eccentric jet in late systole
Tariq[157]	1988–2001		- definition should include structural changes such as leaflet thickening, redundancy, annular dilatation, and chordal elongation
McKay[158]	1989–2001		
Garg[186]	1992–2001		
Tariq[159]	1997–2001		
Cecchi[160]	2000–2001		
Rehman[187]	2000–2001		
Chu[96]	1997–2002		
Yousuf[97]	2000–2002		

Ferreiros[77]	2001–2002		
Heiro[210,211]	1980–2004	+ Speckle tracking (strain (2004))[45,46]	
Hill[102]	2000–2004		
Yiu[246]	1995–2005		
Correa de Sa[107]	1970–2006		AHA/ACC 2006[176]: Clinical: - principal auscultatory feature is the midsystolic click (a high-pitched sound of short duration), may be followed by a late systolic murmur that is usually medium to high-pitched and loudest at the cardiac apex - no further testing is recommended without clinical signs ECG: - usually normal - non-specific ST-T wave changes, T-wave inversions, prominent Q waves, and prolongation of the QT interval also occur Echo: - 2D and Doppler echo is the most useful non-invasive test for defining MVP - valve prolapse of 2 mm or more above the mitral annulus in the long-axis parasternal view and other views, especially when the leaflet coaptation occurs on the atrial side of the annular plane, indicates a high likelihood of MVP - leaflet thickness of 5 mm or more indicates abnormal leaflet thickness and its added presence makes MVP even more certain - leaflet redundancy is often associated with an enlarged mitral annulus and elongated chordae tendineae - absence or presence of MR is an important consideration and MVP is more likely when MR is detected as a high-velocity eccentric jet in late systole
Knudsen[247]	2000–2006		
Math[248]	2004–2006		
Tugcu[110]	1997–2007		
Assiri[162]	2002–2007		
Wong[113]	2002–2007		
Scudeller[249]	2004–2008		
Castillo[250]	1987–2009		
Nakagawa[251]	1990–2009		
Li[215]	1998–2009		
Sun[252]	2000–2009		
Nakatani[163]	2007–2009		
Hajihossainlou[253]	1995–2010		
Lu[217]	1998–2010		
Poesen[127]	2003–2010		
Gupta[128]	2005–2010		
Cecchi[165]	2007–2010		
Senthilkumar[218]	2008–2010		
Sadaka[219]	2009–2010		
Ma[166]	2002–2011		
Al Abri[254]	2006–2011		
Collins[168]	2008–2011		
Turak[135]	2009–2011		
Elbey[221]	2005–2012	3D echocardiography recommendations were published by EAE/ASE (2012)[47]	
Watt[255]	2010–2012		
Gupta[140]	2010–2013		
Jain[188]	2011–2013		

Table 9 – Echocardiographic definitions of MVP for the discussed literature

2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; CW: continuous wave; EAE/ASE: European Association of Echocardiography/American Society of Echocardiography; ECG: electrocardiogram; MR: mitral regurgitation; MVP: mitral valve prolapse; PW: pulsed wave; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography

Definition of MVP Today: (AHA/ACC 2014[2])

In contrast to the AHA/ACC 2006 guidelines[5], MVP is not precisely described in the 2014 guidelines but subsumed under 'primary MR'.

Figure 22 – Definition of MVP today

AHA/ACC: American Heart Association/American College of Cardiology; MR: mitral regurgitation; MVP: mitral valve prolapse

7.5.1.4 Summary of Results

We identified six studies showing that a history of MVP was associated with a higher risk of IE. One study was excluded because of small patient numbers.[224] Two studies reported an odds ratio of approximately 8,[20,226] one an odds ratio of 3,[225] another an odds ratio of 6.7,[223] and another an odds ratio of 19.2.[9] However, all studies were performed prior to the release of the modified Duke criteria (published 2000).

A total of 110 studies were identified that published descriptive statistics on the proportion of patients with MVP in newly diagnosed IE cases. Of these studies, 20 (18.2%) included patients in the study after the publication of the modified Duke criteria. A paired two-tailed t-test of the number of studies published before and after 2001 was highly significant, with a p-value of <0.0001. The mean number of patients included in the 110 studies was 160 (median 111, IQR 72–202), in the studies prior to 2001 was 158 (median 122, IQR 68–210), and in the studies after 2001 was 166 (median 107, IQR 81–139). Of the 110 studies, the mean proportion of patients with MVP was 8.5% (median 7.7%, IQR 4.4%–11.4%). The distribution prior to 2001 was as follows: mean 8.8%, median 8.1%, IQR 4.4%–11.5%. After 2001, the numbers were as follows: mean 7.28%, median 6.7%, IQR 4.4%–10.5%. The differences between the groups were not significant in an unpaired t-test. The dot plot graph shows a cloud consisting of studies with a sample size of less than 200 and a prevalence ranging from 1% to 13%.

The 1998 definition stated that there was no consensus on the 2D echocardiographic criteria for MVP and no single view should be considered diagnostic.[176] Valve prolapse of ≥2 mm, leaflet thickness (increasing certainty with thickness ≥5 mm), and redundancy were, however, diagnostic criteria. The guidelines in 2006 changed in that the long-axis parasternal view was mentioned first and the disagreement concerning the reliability of the echocardiographic appearance of anterior leaflet billowing, only observed in the four-chamber view, was emphasised. In 1987, Levine et al.[263] found that the mitral annulus is not a plane but in particular a 'saddle-shaped' structure. The M-Mode

technique would not satisfy that anatomical fact in a supportive way. The authors were ultimately not able to propose a certain view to diagnose MVP, but they stated that it would be judicious to rely on the parasternal long-axis view because overdiagnosis of MVP could be avoided. The strict use of the parasternal long axis has the limitation that only the A2 and P2 are well seen in this axis and prolapse can involve any other part of the valve.[264] Meanwhile, the echo technique improved and with 3D echocardiography, we are now able to detect MVP even more precisely. Thus, from today's perspective, there is a tendency to believe that the prevalence of MVP was overestimated prior to the publication of modified Duke criteria. Nonetheless, we cannot judge the influence of technique development on the diagnosis of MVP as a risk factor for IE, despite the numerous publications.

In the preliminary meta-analysis, the proportion of patients with IE and mitral valve stenosis (MS) as an underlying condition was 7.2% (95% CI 6.8%–7.6%) for a fixed effects model and 7.5% (95% CI 6.3%–8.7%) in a random effects model. As a few studies contributed greatly to the overall heterogeneity, a second meta-analysis with stricter clinical inclusion/exclusion criteria is planned.

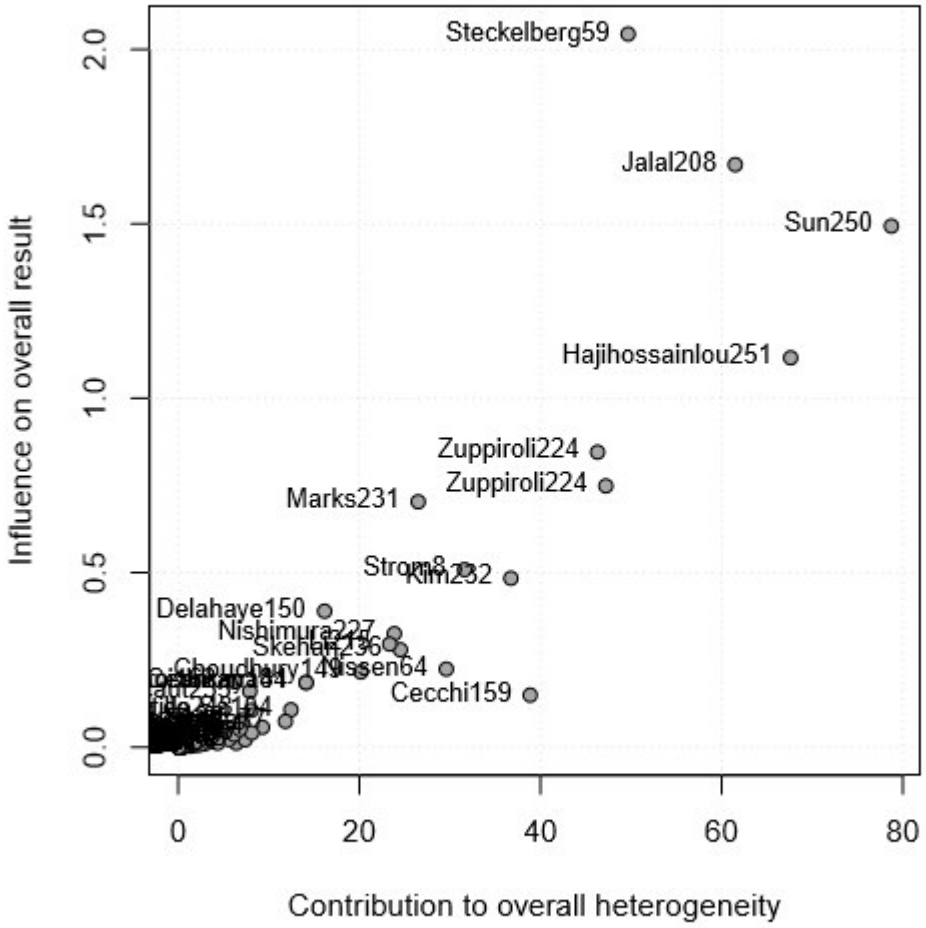

Figure 23 – Heterogeneity in meta-analysis for MVP as an underlying condition for IE

IE: infective endocarditis; MVP: mitral valve prolapse

7.5.2 Mitral Valve Stenosis (MS)

Of the 207 articles considered relevant after the literature review, 23 mentioned MS.

7.5.2.1 Descriptive Statistics

Reference	Time	Place	Patients with (NV)IE	Cases (%) with MS	% with MS	Study Design
Falase[177]	1961–1970	Nigeria	90	5	5.6%	Retrospective, single centre
Bailey[178]	1962–1971	Australia	210	9	4.3%	Retrospective, single centre
Singham[179]	1968–1977	Malaysia	101	3	3.0%	Retrospective, single centre
Hodes[148]	1977–1985	Ethiopia	51	3	5.9%	Retrospective, single centre
Mansur[149]	1978–1986	Brazil	287	11	3.8%	Retrospective, single centre
Blackett[181]	1984–1986	Cameroon	20	4	20.0%	Prospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	3	0.9%	Prospective epidemiologic study, multicentre
Iga[183]	1980–1989	Japan	32	2	6.3%	Retrospective, single centre
Thamlikitkul[150]	1982–1989	Thailand	75	13	17.3%	Retrospective, single centre
Roberts[70]	1954–1991	USA	104	4	3.8%	Retrospective, multicentre
Delahaye[71]	1990–1991	France	415	4	1.0%	Prospective survey, multicentre
Benn[152]	1984–1993	Denmark	62	8	12.9%	Retrospective, multicentre
Werner[76]	1989–1993	Germany	106	6	5.7%	Retrospective, single centre
Cheng[199]	1994–1999	Australia	40	2	5.0%	Retrospective, multicentre
Castillo[93]	1987–2001	Spain	154	13	8.5%	Prospective observational, multicentre
Tariq[157]	1988–2001	Pakistan	159	1	0.6%	Retrospective, single centre
Tariq[159]	1997–2001	Pakistan	66	5	8.0%	Retrospective, single centre
Cecchi[160]	2000–2001	Italy	67	2	3.0%	Prospective, multicentre
Assiri[162]	2002–2007	Saudi Arabia	44	12	27.3%	Retrospective, single centre
Dzupova[118]	2007–2008	Czech Republic	134	1	0.7%	Prospective, multicentre

Leone[122]	2004–2009	Italy	753	3	0.4%	Prospective, multicentre
Nakatani[163]	2007–2009	Japan	513	12	2.3%	Prospective survey, multicentre
Cecchi[165]	2007–2010	Italy	677	17	2.5%	Prospective, multicentre

Table 10 – Literature for MS

MS: mitral valve stenosis; NVIE: native valve infective endocarditis

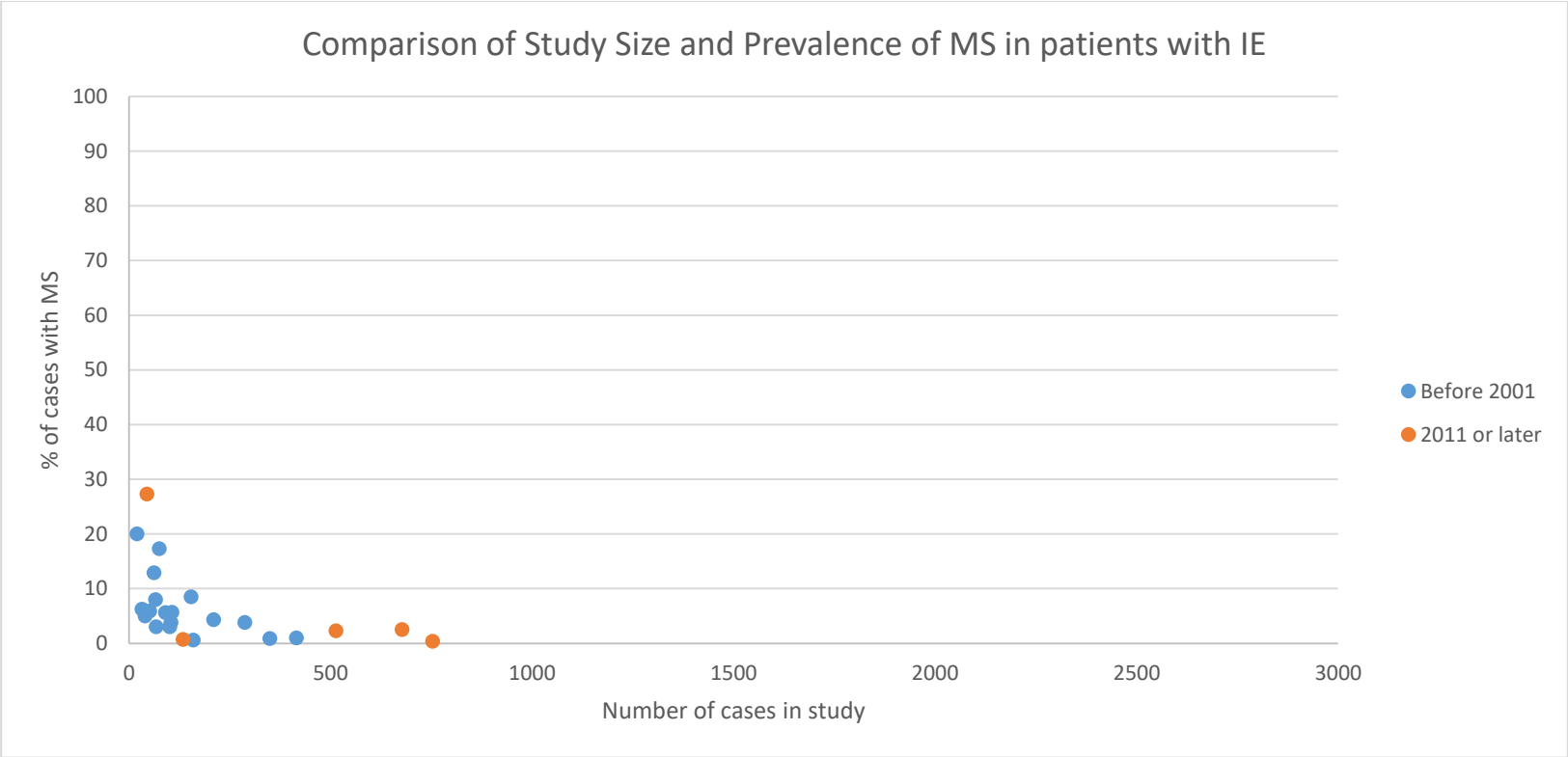

Figure 24 – Comparison of study size with prevalence of MS in patients with IE and in association with IE criteria prior to and after modified Duke criteria

IE: infective endocarditis; MS: mitral valve stenosis

7.5.2.2 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Falase[177]	1961–1970	M-Mode (1954)[26]	Kennedy et al. (1970)[265]: MVA < 2.5 cm^2
Bailey[178]	1962–1971		
Singham[179]	1968–1977	+ B-Mode (2D (1975))[34]	
Hodes[148]	1977–1985		

Mansur[149]	1978–1986	+ Doppler (CW (1979),[36,37] PW (1982)),[40] TOE (1983)[41]	
Blackett[181]	1984–1986		
Van der Meer[8]	1986–1988		Jaffe et al. (1988)[191]: Severe: MVA < 1.5 cm^2, MPG ≥ 12 mmHg
Iga[183]	1980–1989		
Thamlikitkul[150]	1982–1989		
Roberts[70]	1954–1991		
Delahaye[71]	1990–1991		
Benn[152]	1984–1993		
Werner[76]	1989–1993		
Cheng[199]	1994–1999	+ TDI (1994)[174,175]	AHA/ACC 1998[176]: Mild: MVA > 1.5 cm^2, mean ΔP < 5 mmHg Moderate: MVA 1.0–1.5 cm^2, mean ΔP ≥ 5 mmHg, sPAP > 50 mmHg Severe: MVA < 1.0 cm^2, sPAP > 60 mmHg
Castillo[93]	1987–2001	+ Real-time 3D first reports in 2001[43,44]	
Tariq[157]	1988–2001		
Tariq[159]	1997–2001		
Cecchi[160]	2000–2001		
Assiri[162]	2002–2007	+ Speckle tracking (strain (2004))[45,46]	AHA/ACC 2006[5]: Mild: mean ΔP < 5 mmHg, sPAP < 30 mmHg, MVA > 1.5 cm^2 Moderate: mean ΔP 5–10 mmHg, sPAP 30–50 mmHg, MVA 1.0–1.5 cm^2 Severe: mean ΔP > 10 mmHg, sPAP > 50 mmHg, MVA < 1.0 cm^2
Dzupova[118]	2007–2008		
Leone[122]	2004–2009		
Nakatani[163]	2007–2009		
Cecchi[165]	2007–2010		

Table 11 – Echocardiographic definitions of MS for discussed literature

ΔP: pressure difference; 2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; CW: continuous wave; MPG: Mean-Pressure-Gradient; MVA: mitral valve area; PW: pulsed wave; sPAP: systolic pulmonary pressure; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography

Definition Today: (AHA/ACC 2014[2])

Mild: MVA > 1.5 cm^2, diastolic PHT < 150 ms

Severe: MVA ≤ 1.5 cm^2, diastolic PHT ≥ 150 ms

Very severe: MVA ≤ 1.0 cm^2, diastolic PHT ≥ 220 ms

Figure 25 – Definition of MS today

AHA/ACC: American Heart Association/American College of Cardiology; MVA: mitral valve area; PHT: pressure half-time

7.5.2.3 Summary of Results

In the literature review, no studies reporting an odds ratio for patients with MS and developing IE were identified.

Twenty-three studies were identified that published descriptive statistics on the proportion of patients with MS in newly diagnosed IE cases. Of these studies, five (21.7%) included patients after the publication of the modified Duke criteria. A paired two-tailed t-test of the number of studies published before and after 2001 was significant, with a p-value of 0.004, although more patients (absolute numbers) were included in studies after the presentation of the Duke criteria. The mean number of patients included in the 23 studies was 196 (median 104, IQR 64–249), in the studies prior to 2001 was 133 (median 96, IQR 63–158), and in the studies after 2001 was 424 (median 513, IQR 134–667). Of the 23 studies, the mean proportion of patients with MS was 6.5% (median 4.3%, IQR 3.2%–7.6%). The distribution prior to 2001 was as follows: mean 6.4%, median 5.3%, IQR 3.2%–7.6%. After 2001, the numbers were as follows: mean 6.6%, median 2.3%, IQR 0.7%–2.5%. The difference between groups was not significant in an unpaired t-test. Similarly, the dot plot graph indicates that with increasing sample size number in the corresponding studies with definitions in accordance with the modified Duke criteria, the prevalence of IE in patients with MS is ≤1%.

MS has been a well-known entity.[266] With the help of echocardiography and especially continuous wave Doppler imaging (CW Doppler, 1979), a non-invasive diagnosis and grading of MS became easier and could be performed bedside. The definition of MS has not changed since the introduction of CW Doppler, but the gradient was made easier to determine. Since then, it cannot be firmly concluded that the imaging technique has influenced the diagnosis of MS as a predisposing heart condition for IE.

In the preliminary meta-analysis, the proportion of patients with IE and MS as an underlying condition was 2.12% (95% CI 1.7%–2.6%) for a fixed effects model and 4.3% (95% CI 2.7%–6.2%) in a random effects model. As a few studies contributed greatly to the overall heterogeneity, a second meta-analysis with stricter clinical inclusion/exclusion criteria is planned.

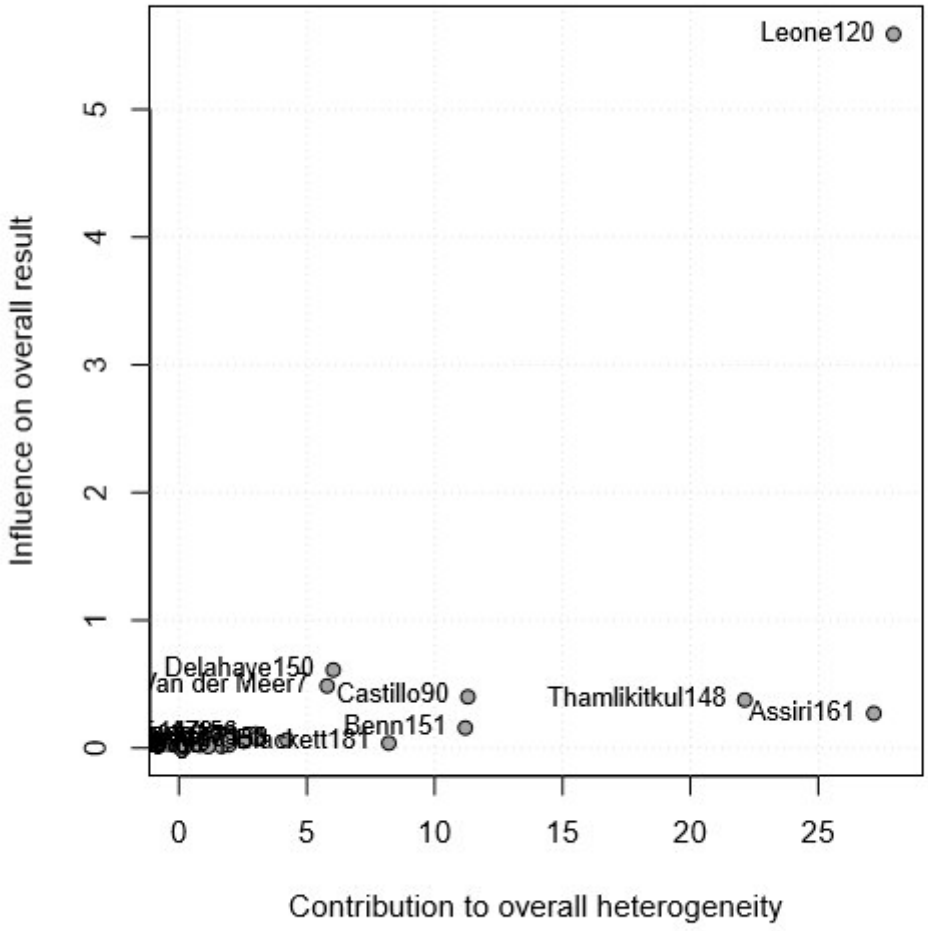

Figure 26 – Heterogeneity in meta-analysis for MS as an underlying condition for IE

IE: infective endocarditis; MS: mitral valve stenosis

7.5.3 Mitral Valve Insufficiency (MI)

Of the 207 articles considered relevant after the literature review, 41 mentioned MI.

7.5.3.1 Descriptive Statistics

Reference	Time	Place	Patients with (NV)IE	Cases with MI	% with MI	Study Design
Falase[177]	1961–1970	Nigeria	90	17	18.9%	Retrospective, single centre
Bailey[178]	1962–1971	Australia	210	22	10.5%	Retrospective, single centre
Lowes[53]	1966–1975	UK	60	18	30.0%	Retrospective survey, single centre
Corrigall[228]	1969–1975	USA	87	18	20.7%	Retrospective, single centre
Singham[179]	1968–1977	Malaysia	101	16	15.8%	Retrospective, single centre
Robbins[145]	1970–1977	USA	56	16	28.6%	Retrospective, single centre
Hodes[148]	1977–1985	Ethiopia	51	4	7.8%	Retrospective, single centre
Mansur[149]	1978–1986	Brazil	287	56	16.0%	Retrospective, single centre
Blackett[181]	1984–1986	Cameroon	20	7	35.0%	Prospective, single centre
Cheng[199]	1979–1987	Taiwan	97	16	16.5%	Retrospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	89	25.5%	Prospective epidemiologic study, multicentre
Agarwal[182]	1987–1988	India	28	2	7.1%	Single centre, probably prospective, but not clearly stated
Iga[183]	1980–1989	Japan	32	11	34.4%	Retrospective, single centre
Nissen[66]	1980–1989	Denmark	132	0	0.0%	Retrospective, multicentre
Thamlikitkul[150]	1982–1989	Thailand	75	35	46.7%	Retrospective, single centre
Manford[184]	1983–1989	UK	33	5	15.2%	Retrospective, single centre
Strom[9]	1988–1990	USA	279	3	1.1%	Population-based, case-control study, multicentre
Choudhury[151]	1981–1991	India	186	9	4.8%	Retrospective, single centre
Delahaye[71]	1990–1991	France	415	51	12.3%	Prospective survey, multicentre

Rognon[74]	1983–1993	Switzerland	179	47	26.3%	Retrospective, multicentre
Werner[76]	1989–1993	Germany	106	5	4.7%	Retrospective, single centre
Netzer[153]	1980–1995	Switzerland	212	38	18.0%	Retrospective, single centre
Lamas[79]	1985–1996	UK	100	5	5.0%	Prospective, single centre
Cheng[155]	1994–1999	Australia	40	7	17.5%	Retrospective, multicentre
Di Filippo[156]	1966–2001	France	153	8	5.2%	Retrospective, single centre
McKay[158]	1989–2001	New Zealand	29	1	3.4%	Retrospective, multicentre
Garg[186]	1992–2001	India	192	3	1.6%	Retrospective, single centre
Tariq[159]	1997–2001	Pakistan	66	2	3.0%	Retrospective, single centre
Cecchi[160]	2000–2001	Italy	67	3	4.5%	Prospective, multicentre
Rehman[187]	2000–2001	Pakistan	30	5	16.7%	Prospective, single centre
Durante-Mangoni[161]	2000–2005	ICE cohort	2759	N/A	38%–57%	Prospective, multicentre (ICE cohort)
Murdoch[105]	2000–2005	ICE cohort	2781	1196	43.0%	Prospective cohort study, multicentre (ICE-PCS)
Math[248]	2004–2006	India	104	10	9.6%	Prospective observational study, single centre
Assiri[162]	2002–2007	Saudi Arabia	44	18	40.9%	Retrospective, single centre
Dzupova[118]	2007–2008	Czech Republic	134	5	3.7%	Prospective, multicentre
Leone[122]	2004–2009	Italy	753	80	10.6%	Prospective, multicentre
Nakatani[163]	2007–2009	Japan	513	145	28.3%	Prospective survey, multicentre
Cecchi[165]	2007–2010	Italy	677	60	8.9%	Prospective, multicentre
Begezsan[167]	2007–2011	Romania	45	17	37.8%	Retrospective, single centre
Elbey[221]	2005–2012	Turkey	148	142	95.9%	Retrospective, multicentre
Jain[188]	2011–2013	India	75	28	37.3%	Prospective observational, single centre

Table 12 – Literature for MI

ICE: International Collaboration on Endocarditis; ICE-PCS: International Collaboration on Endocarditis-Prospective Cohort Study; MI: mitral valve insufficiency/regurgitation; N/A: not available; NVIE: native valve infective endocarditis

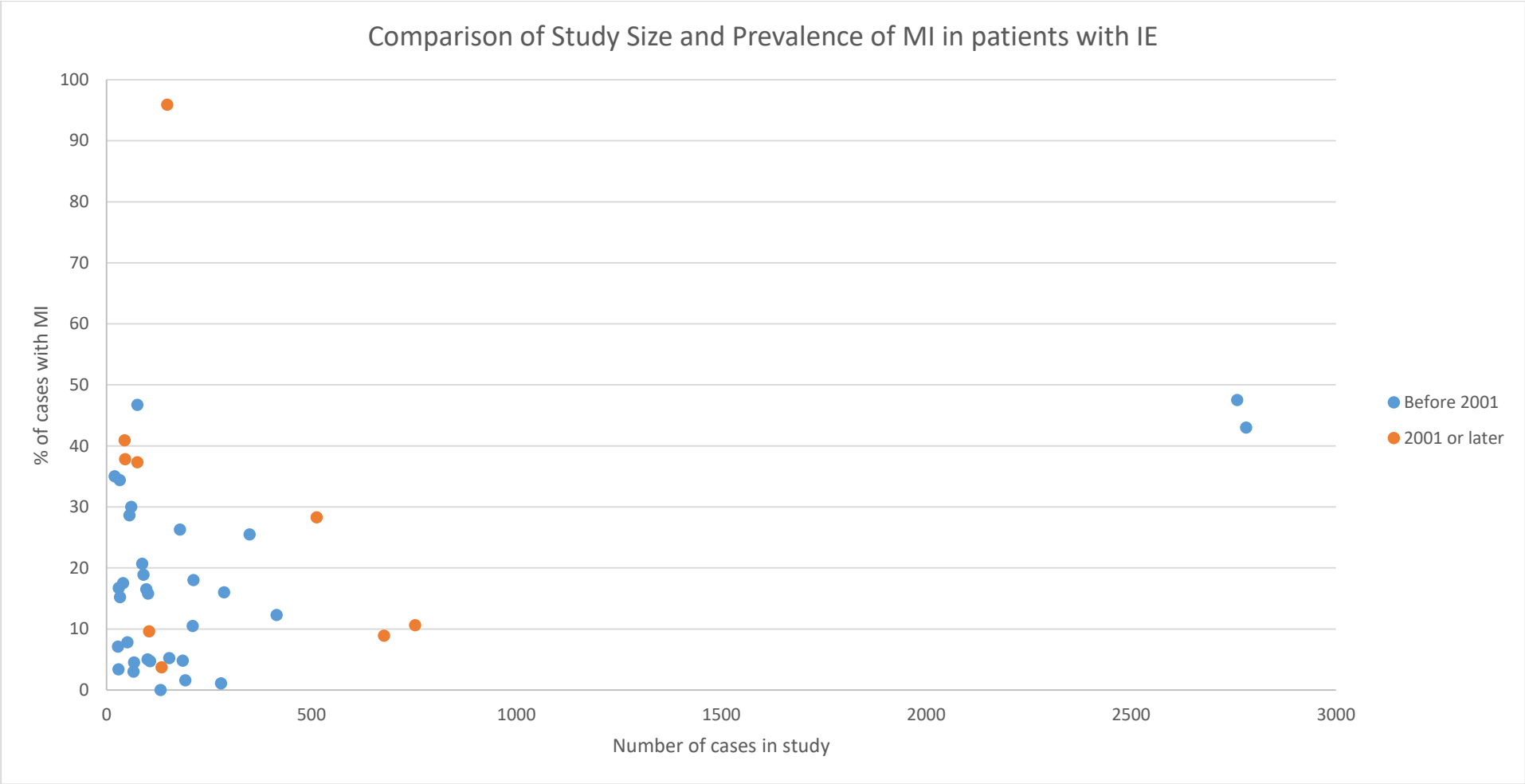

Figure 27 – Comparison of study size with prevalence of MI in patients with IE and in association with IE criteria prior to and after modified Duke criteria

IE: infective endocarditis; MI: mitral valve insufficiency/regurgitation

7.5.3.2 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Falase[177]	1961–1970	M-Mode (1954)[26]	Kennedy et al. 1970[265]: MR > 2L/min
Bailey[178]	1962–1971		
Lowes[53]	1966–1975	+ B-Mode (2D (1975))[34]	
Corrigall[228]	1969–1975		
Singham[179]	1968–1977		
Robbins[145]	1970–1977		
Hodes[148]	1977–1985	+ Doppler (CW (1979),[36,37] PW (1982)),[40] TOE (1983)[41]	
Mansur[149]	1978–1986		
Blackett[181]	1984–1986		
Cheng[199]	1979–1987		
Van der Meer[8]	1986–1988		Jaffe et al. 1988[191]: Severe: RF ≥ 30%, cardiac catheterisation ≥ 3+
Agarwal[182]	1987–1988		
Iga[183]	1980–1989		
Nissen[66]	1980–1989		
Thamlikitkul[150]	1982–1989		
Manford[184]	1983–1989		
Strom[9]	1988–1990		
Choudhury[151]	1981–1991		
Delahaye[71]	1990–1991		
Rognon	1983–1993		
Werner[76]	1989–1993		
Netzer[153]	1980–1995	+ TDI (1994)[174,175]	
Lamas[79]	1985–1996		
Cheng[155]	1994–1999		
Di Filippo[156]	1966–2001	+ Real-time 3D first reports in 2001[43,44]	
McKay[158]	1989–2001		
Garg[186]	1992–2001		
Tariq[159]	1997–2001		

Cecchi[160]	2000–2001		
Rehman[187]	2000–2001		
Durante-Mangoni[161]	2000–2005	+ Speckle tracking (strain (2004))[45,46]	
Murdoch[105]	2000–2005		
Math[248]	2004–2006		AHA/ACC 2006[5]: Mild: jet < 4 cm^2 or < 20% LA, VC < 0.3 cm, RVol < 30 ml, RF < 30%, ERO < 0.2 cm^2 Moderate: jet > mild but no severe MI, VC 0.3–0.69 cm, RVol 30–59 ml, RF 30%–49%, ERO 0.2–0.39 cm^2 Severe: jet > 40% LA or wall impinging, VC ≥ 0.7 cm, RVol ≥ 60 ml, RF ≥ 50%, ERO ≥ 0.40 cm^2
Assiri[162]	2002–2007		
Dzupova[118]	2007–2008		
Leone[122]	2004–2009		
Nakatani[163]	2007–2009		
Cecchi[165]	2007–2010		
Begezsan[167]	2007–2011		
Elbey[221]	2005–2012	+ 3D echocardiography recommendations were published by EAE/ASE (2012)[47]	
Jain[188]	2011–2013		

Table 13 – Echocardiographic definitions of MI for discussed literature

2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; CW: continuous wave; EAE/ASE: European Association of Echocardiography/American Society of Echocardiography; ERO: effective regurgitant orifice; LA: Left atrium; MI: mitral valve insufficiency/regurgitation; MR: mitral regurgitation; PW: pulsed wave; RF: regurgitant fraction; RVol: regurgitant volume; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography; VC: vena contracta

Definition of MI Today: (AHA/ACC 2014[2])

At risk: jet < 20% LA on Doppler, VC < 0.3 cm

Progressive: central jet 20%–40% LA, VC < 0.7 cm, RVol < 60 ml, RF < 50%, ERO < 0.4 cm^2

Severe: central jet > 40% LA, VC ≥ 0.7 cm, RVol ≥ 60 ml, RF ≥ 50%, ERO ≥ 0.40 cm^2

Figure 28 – Definition of MI today

AHA/ACC: American Heart Association/American College of Cardiology; ERO: effective regurgitant orifice; LA: left atrium; MI: mitral valve insufficiency/regurgitation; RF: regurgitant fraction; RVol: regurgitant volume; VC: vena contracta

7.5.3.3 Summary of Results

In the literature review, no studies reporting analytical statistics for patients with MI for developing IE could be identified.

Forty-one studies were identified that published descriptive statistics on the proportion of patients with MI in newly diagnosed IE cases. Of these studies, nine (22%) included patients in the study after the publication of the modified Duke criteria. A paired two-tailed t-test of the number of studies published before and after 2001 was significant, with a p-value pf 0.0001. The mean number of patients included in the 41 studies was 288 (median 101, IQR 56–210), in the studies prior to 2001 was 291 (median 99, IQR 55–197), and in the studies after 2001 was 277 (median 134, IQR 75–513). Of the 41 studies, the mean proportion of patients with a history of previous IE was 19.9% (median 16%, IQR 5.2%–28.6%). The distribution prior to 2001 was as follows: mean 17%, median 15.9%, IQR 5%–25.7%. After 2001, the numbers were as follows: mean 30.3%, median 28.3%, IQR 9.6%–37.8%. The difference between the groups was not significant in an unpaired t-test. The dot plot indicates that there are many studies with a publication bias. This may be also be because the research question is difficult to answer in this constellation. For example, some studies may represent that their patients developed MI because of IE and not that MI was a risk factor for developing IE.

The definitions of the graduation of MI was implemented rather late in the guidelines 2006,[5] again after the recommendations by ASE.[192] Echo criteria were mentioned earlier in the AHA guidelines in 1998 concerning the time of surgery and considering LV diameters.[176] It can be concluded that the development of echo techniques and, with that, improvements in imaging most likely played an important role in defining MI.

In the preliminary meta-analysis, the proportion of patients with IE and MI as an underlying condition was 2.7% (95% CI 2.6%–2.7%) for a fixed effects model and 1.7% (95% CI 1.1%–2.3%) in a random

effects model. As a few studies contributed greatly to the overall heterogeneity, a second meta-analysis with stricter clinical inclusion/exclusion criteria is planned.

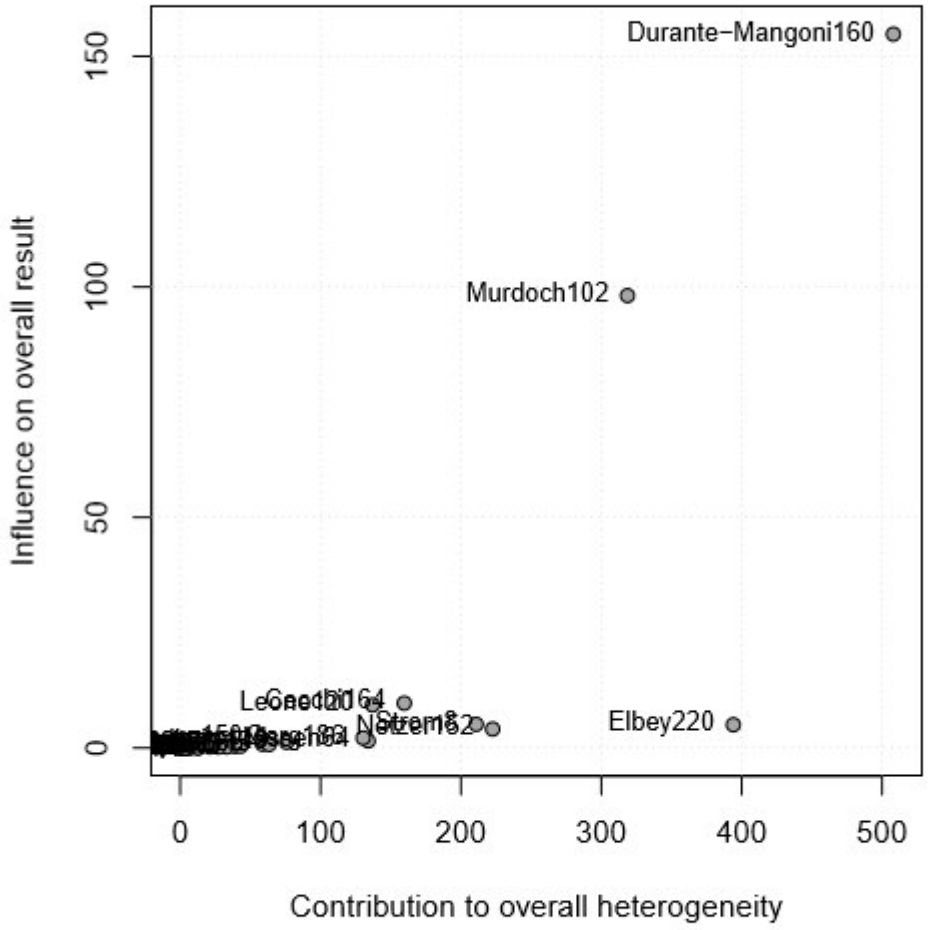

Figure 29 – Heterogeneity in meta-analysis for MI as an underlying condition for IE

IE: infective endocarditis; MI: mitral valve insufficiency/regurgitation

7.6 Tricuspid Valve

Of the 207 articles considered relevant after the literature review, nine mentioned TI or TS.

7.6.1 Descriptive Statistics

Reference	Time	Place	Patients with IE	Cases with TI/TS	% with TI/TS	Study Design
Blackett[181]	1984–1986	Cameroon	20	1	5%	Prospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	19	5.4%	Prospective epidemiologic study, multicentre
Thamlikitkul[150]	1982–1989	Thailand	75	8	10.7%	Retrospective, single centre
Delahaye[71]	1990–1991	France	415	1	0.2%	Prospective survey, multicentre
Garg[186]	1992–2001	India	192	4	2.1%	Retrospective, single centre
Rehman[187]	2000–2001	Pakistan	30	1	3.3%	Prospective, single centre
Assiri[162]	2002–2007	Saudi Arabia	44	8	18.2%	Retrospective, single centre
Nakatani[163]	2007–2009	Japan	513	13	2.5%	Prospective survey, multicentre
Begezsan[167]	2007–2011	Romania	45	7	15.5%	Retrospective, single centre

Table 14 – Literature for TI/TS

IE: infective endocarditis; TI: tricuspid valve insufficiency/regurgitation; TS: tricuspid valve stenosis

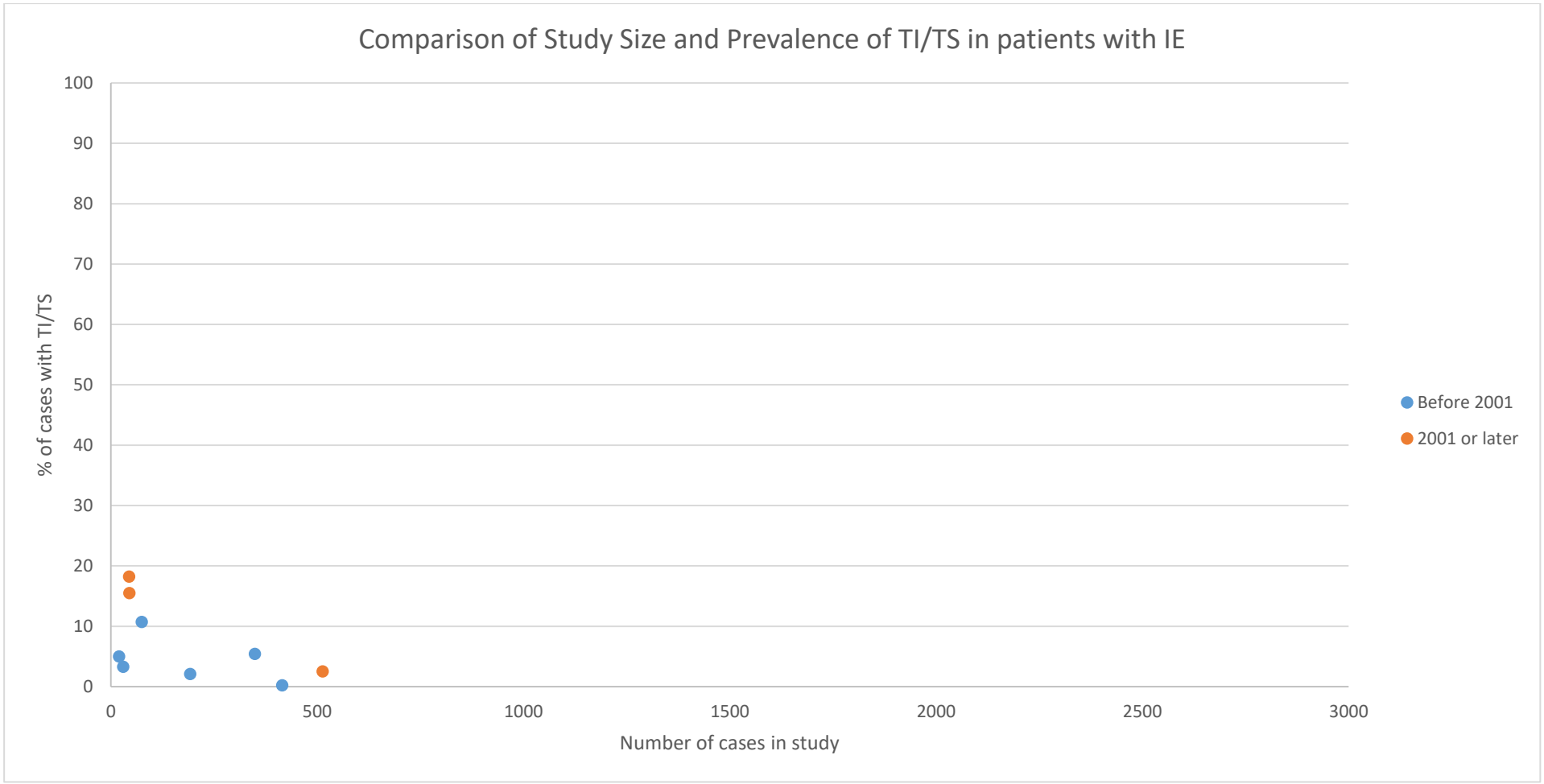

Figure 30 – Comparison of study size with prevalence of TI/TS in patients with IE and in association with IE criteria prior to and after modified Duke criteria

IE: infective endocarditis; TI: tricuspid valve insufficiency/regurgitation; TS: tricuspid valve stenosis

7.6.1.1 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Blackett[181]	1984–1986	M-Mode (1954),[26] B-Mode (2D (1975)),[34] Doppler (CW (1979),[36,37] PW (1982)),[40] TOE (1983)[41]	Various publications 1970s and 1980s[267-271]: Insufficiency: clinical and ECG definition of *severe* insufficiency, mostly post-trauma and Ebstein's anomaly Stenosis: no data
Van der Meer[8]	1986–1988		
Thamlikitkul[150]	1982–1989		
Delahaye[71]	1990–1991		
Garg[186]	1992–2001	+ TDI (1994),[174,175] Real-time 3D first reports in 2001[43,44]	AHA/ACC 1998[176]: not defined
Rehman[187]	2000–2001		
Assiri[162]	2002–2007	+ Speckle tracking (strain (2004))[45,46]	AHA/ACC 2006[5]: Severe insufficiency: VC > 0.7 cm, hepatic vein flow: systolic reversal Severe stenosis: valve area < 1.0 cm^2
Nakatani[163]	2007–2009		
Begezsan[167]	2007–2011		

Table 15 – Echocardiographic definitions of TI/TS for discussed literature

2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; CW: continuous wave; ECG: electrocardiogram; PW: pulsed wave; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography; VC: vena contracta

Definition of TI/TS Today: (AHA/ACC 2014[2])

Insufficiency

Mild: central jet area < 5 cm^2, VC not defined

Moderate: central jet 5–10 cm^2, VC not defined but <0.7 cm, hepatic vein flow: systolic blunting

Severe: central jet > 10 cm^2, VC > 0.7 cm, hepatic vein flow: systolic reversal

Stenosis

Severe: PHT ≥ 190 ms, valve area ≤ 1.0 cm^2

Figure 31 – Definition of TI/TS today

AHA/ACC: American Heart Association/American College of Cardiology; PHT: pressure half-time; TI: tricuspid valve insufficiency/regurgitation; TS: tricuspid valve stenosis; VC: vena contracta

7.6.2 Summary of Results

No studies reporting an odds ratio for patients with TI or TS for developing IE could be identified.

Nine studies were identified that published descriptive statistics on the proportion of patients with a history of IE in newly diagnosed IE cases. Of these studies, three included patients in the study after the publication of the modified Duke criteria. The mean number of patients included in the nine studies was 187 (median 75, IQR 44–349), in the studies prior to 2001 was 180 (median 134, IQR 41–310), and in the studies after 2001 was 201 (median 45, IQR 44.5–279). Of the nine studies, the mean proportion of patients with TS or TI was 7% (median 5%, IQR 2.5%–10.7%). The distribution prior to 2001 was as follows: mean 4.5%, median 4.2%, IQR 2.4%–5.3%. After 2001, the numbers were as follows: mean 12.1%, median 15.5%, IQR 9%–16.9%. The dot plot graph indicates that the prevalence is low and that at least three studies may have a publication bias.

Severe TI/TS was first described in the guidelines 2006.[272] The recent guidelines from 2014[2] gave a more precise definition of the different grades of TI/TS (defining mild, moderate, and severe), whereas for the clinician, mild and moderate play a subordinate role. Evolution of echocardiography techniques was crucial for the new definitions, but even more for finding the real cause of TI, which is often secondary, particularly in the context of right ventricle dysfunction and dilatation. The

relevance of the development of this technique in light of the few studies and low incidence of IE is difficult to estimate.

In the preliminary meta-analysis, the proportion of patients with IE and TI/TS as an underlying condition was 2.3% (95% CI 1.6%–3.2%) for a fixed effects model and 4.9% (95% CI 1.9%–9.0%) in a random effects model. A few studies contributed greatly to the overall heterogeneity. Because of the limited number of studies, however, no further evaluation is planned.

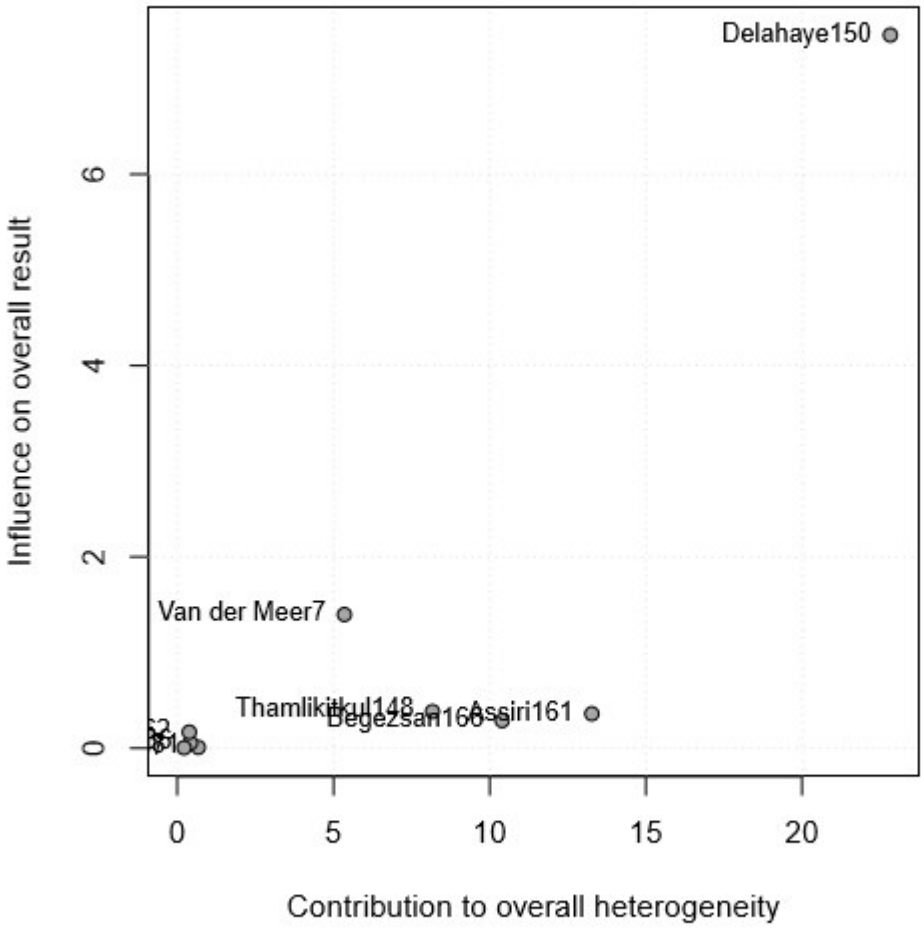

Figure 32 – Heterogeneity in meta-analysis for TI/TS as an underlying condition for IE

IE: infective endocarditis; TI: tricuspid valve insufficiency/regurgitation; TS: tricuspid valve stenosis

7.7 Pulmonary Valve

Of the 207 articles considered relevant after the literature review, 18 mentioned PS or PI.

7.7.1 Analytical Statistics

Verheugt et al.[141] described patients from the CONCOR national registry for adults with congenital heart disease from the Netherlands. Of 778 patients with congenital PS, three (0.39%) developed IE. This equals a hazard ratio of 1.1 (95% CI 0.3–4.0).

7.7.2 Descriptive Statistics

Dodo et al.[273] reported 186 patients with disease resulting in high-velocity flow over pulmonary and/or tricuspid valves. They found only one patient with IE (and one IVDU), resulting in a rate of 0.61 episodes per 1000 patient-years, or 0.54% of patients. They stated that those instances might be at low risk or no risk for IE.

Gersony et al.[142] described 592 patients with PS from the Second Natural History Study of Congenital Heart Defects conducted in the USA between 1958 and 1965. They reported a prevalence rate of 16.9 per 10,000 patients (95% CI 0.4–94.1). Follow-up was conducted for 10,688 person-years, with an incidence rate of 0.9 per 10,000 person-years (95% CI 0.02–5.2). They stated that this is a very low incidence of infection.

Hayes et al.[274] described 592 patients with PS from the Second Natural History Study of Congenital Heart Defects conducted in the USA between 1958 and 1969. They reported that IE did not occur during follow-up and concluded that IE is a rare condition for patients with PS.

Reference	Time	Place	Patients with (NV)IE	Cases with PI or PS	% with PI/PS	Study Design
Gersony[142]	1958–1965	USA	592	1	0.2%	Prospective cohort study, multicentre
Cassel[195]	1974–1976	South Africa	40	1	2.5%	Retrospective, single centre
Singham[179]	1968–1977	Malaysia	101	2	2.0%	Retrospective, single centre
Sawae[275]	1964–1983	Japan	91	2	2.2%	Retrospective, multicentre
Woo[198]	1971–1986	Hong Kong	176	2	1.1%	Mixed retrospective and prospective, single centre
Mansur[149]	1978–1986	Brazil	287	2	0.7%	Retrospective, single centre
Van der Meer[8]	1986–1988	Netherlands	349	1	0.3%	Prospective epidemiologic study, multicentre
Verheul[276]	1966–1991	Netherlands	141	15	10.6%	Retrospective, single centre
Choudhury[151]	1981–1991	India	186	2	1.1%	Retrospective, single centre
Lamas[79]	1985–1996	UK	100	1	1.0%	Retrospective, single centre
Jalal[203]	1982–1997	India	466	2	0.4%	Retrospective, single centre
Dodo[273]	Before 1998		186	1	0.5%	Prospective, observational, single centre
Di Filippo[156]	1966–2001	France	153	1	0.6%	Retrospective, single centre
Rehman[187]	2000–2001	Pakistan	30	1	3.3%	Prospective, single centre
Nashmi[99]	1993–2003	Saudi Arabia	47	2	4.2%	Retrospective, single centre
Nakatani[163]	2007–2009	Japan	513	1	0.2%	Prospective survey, multicentre
Verheugt[141]	Before 2011	The Netherlands	778	3	0.4%	Prospective cohort study, multicentre

Table 16 – Literature for PI/PS: Patients with IE with PS/PI as an underlying condition

IE: infective endocarditis; NVIE: native valve infective endocarditis; PI: pulmonary valve insufficiency/regurgitation; PS: pulmonary valve stenosis

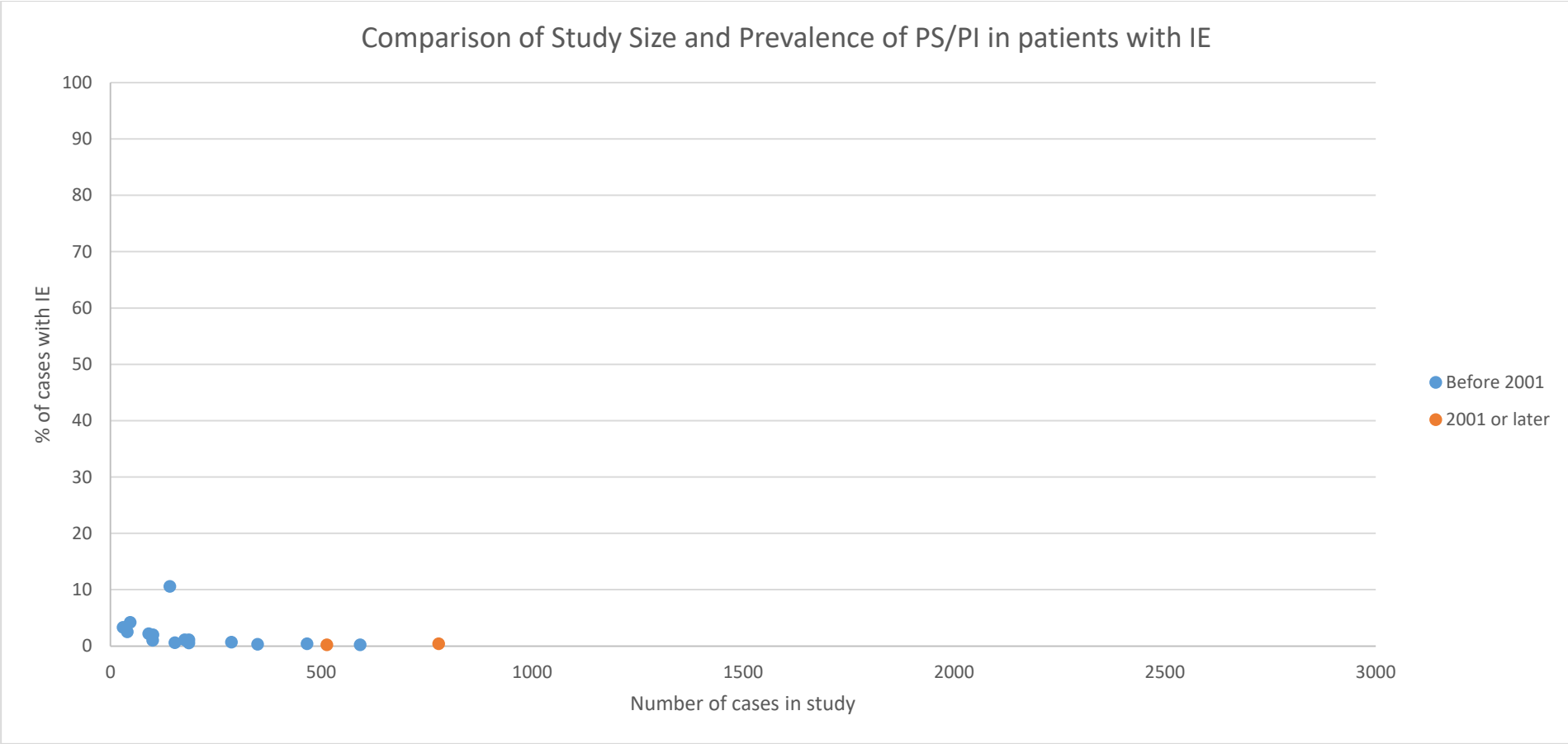

Figure 33 – Comparison of study size with prevalence of PI/PS in patients with IE and in association with IE criteria prior to and after modified Duke criteria

IE: infective endocarditis; PI: pulmonary valve insufficiency/regurgitation; PS: pulmonary valve stenosis

7.7.2.1 Review of Available Echo Techniques

Reference	Time	Available Echo Technique	Definition at the Time
Gersony[142]	1958–1965	M-Mode (1954),[26]	
Cassel[195]	1974–1976	+ B-Mode (2D (1975))[34]	Johnson et al. (1972)[277]: Stenosis: Mild: right ventricle systolic pressure > 50 mmHg Moderate: 50–99 mmHg Severe: > 100 mmHg Insufficiency: no data
Singham[179]	1968–1977		
Sawae[275]	1964–1983	+ Doppler (CW (1979),[36,37] PW (1982)),[40] TOE (1983)[41]	
Woo[198]	1971–1986		
Mansur[149]	1978–1986		
Van der Meer[8]	1986–1988		
Verheul[276]	1966–1991		
Choudhury[151]	1981–1991		
Lamas[79]	1985–1996	+ TDI (1994)[174,175]	
Jalal[203]	1982–1997		
Dodo[273]	Before 1998		
Di Filippo[156]	1966–2001	+ Real-time 3D first reports in 2001[43,44]	AHA/ACC 1998[176]: not defined
Rehman[187]	2000–2001		
Nashmi[99]	1993–2003		
Nakatani[163]	2007–2009	+ Speckle tracking (strain (2004))[45,46]	AHA/ACC 2006[5]: Severe insufficiency: colour jet fills outflow tract; dense continuous wave Doppler signal with a steep deceleration slope Severe stenosis: V_{max} > 4 m/s or maximum gradient > 60 mmHg
Verheugt[141]	Before 2011		

Table 17 – Echocardiographic definitions of PI/PS for discussed literature

2D: two-dimensional; 3D: three-dimensional; AHA/ACC: American Heart Association/American College of Cardiology; CW: continuous wave; PW: pulsed wave; TDI: tissue Doppler imaging; TOE: transoesophageal echocardiography; V_{max}: maximum velocity.

Definition of PS/PI Today: (AHA/ACC 2014[2])

Severe insufficiency: colour jet fills right ventricular outflow tract, CW jet dense, steep deceleration, may terminate abruptly

Severe stenosis: V_{max} > 4 m/s, peak instantaneous gradient > 64 mmHg

Figure 34— Definition of PS/PI today

AHA/ACC: American Heart Association/American College of Cardiology; CW: continuous wave; PI: pulmonary valve insufficiency/regurgitation; PS: pulmonary valve stenosis; V_{max}: maximum velocity

7.7.3 Summary of Results

We identified one study analysing the risk of developing IE in patients with congenital PS, reporting a hazard ratio of 1.1.[141] No studies for PI or other aetiologies of PS were identified in the literature review.

Seventeen studies were identified that published descriptive statistics on the proportion of patients with a history of IE in newly diagnosed IE cases. Of these studies, two included patients in the study after the publication of the modified Duke criteria. A paired two-tailed t-test of the number of studies published before and after 2001 was significant, with a p-value of 0.0002. The mean number of patients included in the 17 studies was 249 (median 176, IQR 100–349), in the studies prior to 2001 was 196 (median 153, IQR 95.5–236.5), and in the studies after 2001 was 645.5 (median 645.5, IQR 579.3–711.8). Of the 17 studies, the mean proportion of patients with a history of previous IE was 1.8% (median 1%, IQR 0.4%–2.2%). The distribution prior to 2001 was as follows: mean 2%, median 1.1%, IQR 0.57%–2.35%. After 2001, the numbers were as follows: mean 0.3%, median 0.3%, IQR 0.2%–0.3%. The difference between groups was not significant in an unpaired t-test. Similarly, the dot plot graph indicated a very low prevalence throughout all studies.

As mentioned earlier (in the chapter on TI/TS [7.6]), the development of echo techniques played a role in defining PI/PS. Regarding the publications listed earlier, PI was first defined in the guidelines in 2006[5] and profited most from advanced echo techniques because, with the help of colour Doppler, PI can be made easily visible. PS is most important when considering congenital heart disease. The clinical role in adults, however, is less important and may result from rare causes, such as carcinoid plaques.[278]

The relevance of this technique development in light of the few studies and low incidence of IE is difficult to estimate.

In the preliminary meta-analysis, the proportion of patients with IE and TI/TS as an underlying condition was 0.4% (95% CI 0.2%–0.7%) for a fixed effects model and 0.9% (95% CI 0.3%–1.7%) in a random effects model. A few studies contributed greatly to the overall heterogeneity. Because of the limited number of studies, however, no further evaluation is planned.

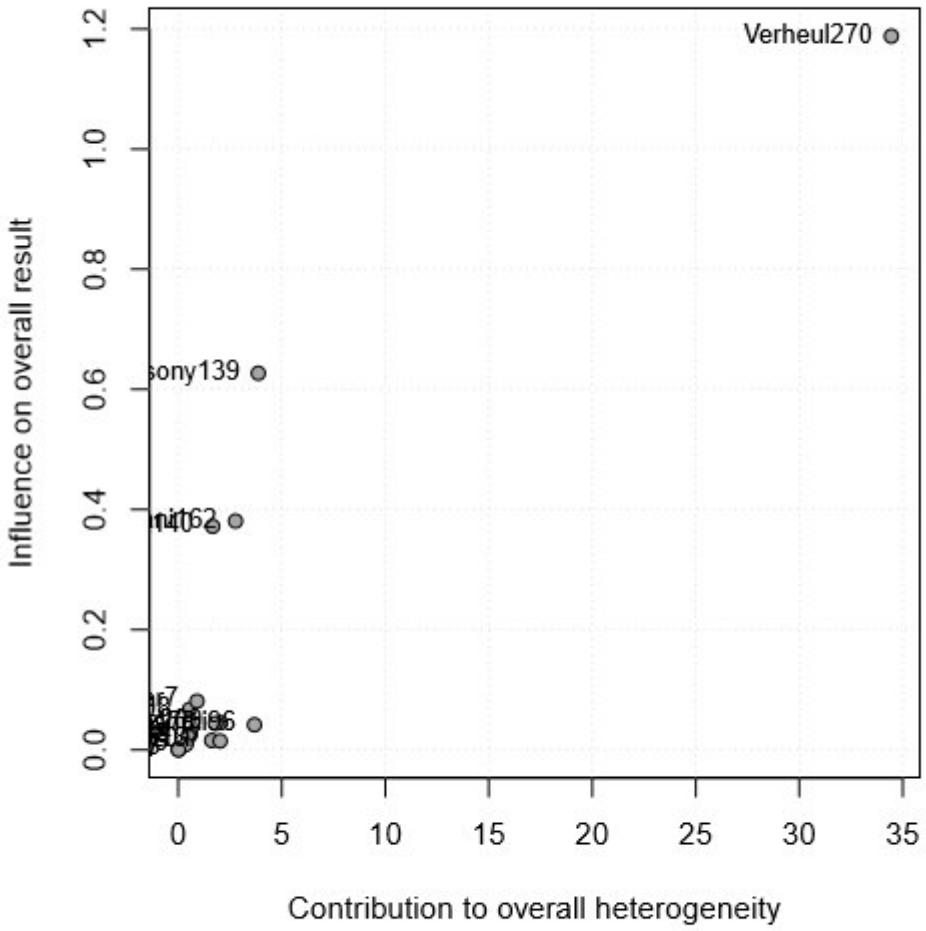

Figure 35 – Heterogeneity in a meta-analysis for PI/PS as an underlying condition for IE

IE: infective endocarditis; PI: pulmonary valve insufficiency/regurgitation; PS: pulmonary valve stenosis

7.8 Questionnaire

In total, 318 questionnaires were received and included for analysis.

7.8.1 Date of final Examination in Medical School

In total, 98% of participants answered this question (**Fehler! Verweisquelle konnte nicht gefunden werden.**, page **Fehler! Textmarke nicht definiert.**). As shown in Figure 36 (page 109), most participants passed their state examination after 2000.

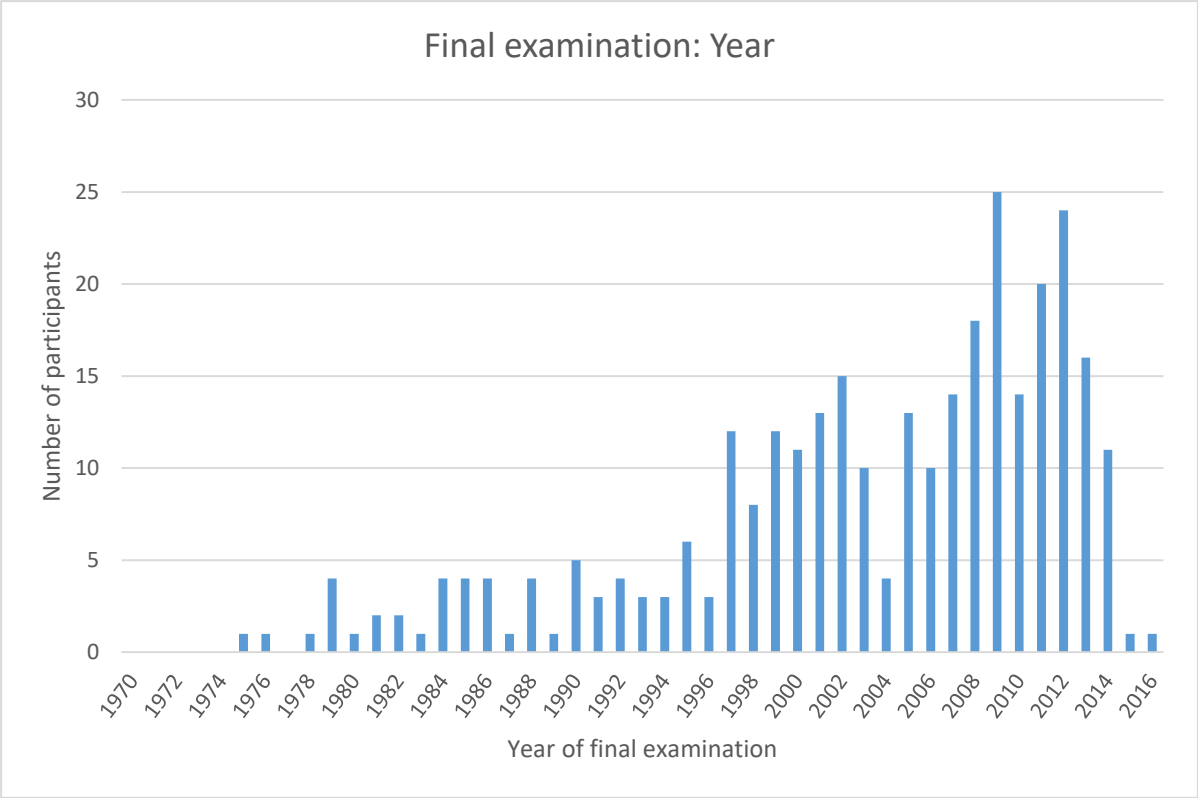

Figure 36 – Year of final examination of participants

To quantify the clinical experience of study participants, we formed three groups: little experience (1–2 years, from 2014), intermediate experience (3–5 years, 2011–2013), and experienced professionals (>5 years, final examination before 2011). This does not account for gap years or years in clinical research, but because of the limited information on the working experience of our study participants, a more detailed analysis is not possible. Thirteen participants (4.2%) had 1–2 years of experience, 60 (19.2%) had 2–5 years of experience, and 237 (75.7%) were very experienced, having clinical experience of more than 5 years.

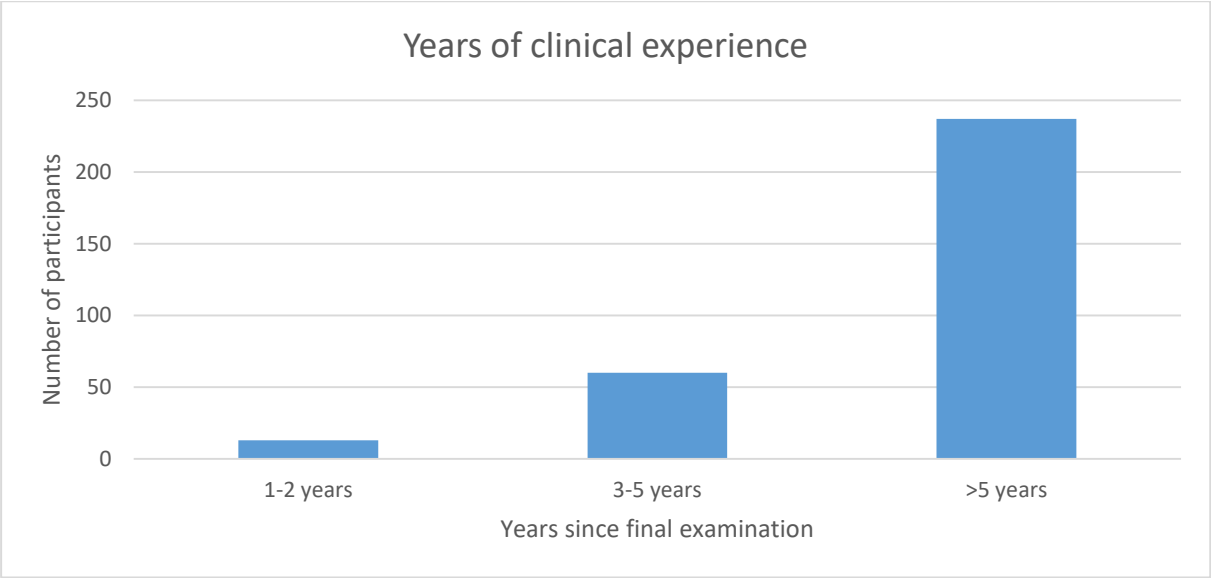

Figure 37 – Years of clinical experience of participants

7.8.2 Appointments of Study Participants

In total, 93.3% of participants responded to the question: What is your current appointment? Of these, 50% were in postgraduate training for a medical speciality. In 31.8% of the questionnaire responders, a double specialisation (i.e. internal medicine and cardiology) was indicated, and in 12.9% of responders, postgraduate training for their second specialisation was notable (data shown below). This is well in line with the majority of our study participants having extensive clinical experience, as noted in the previous section.

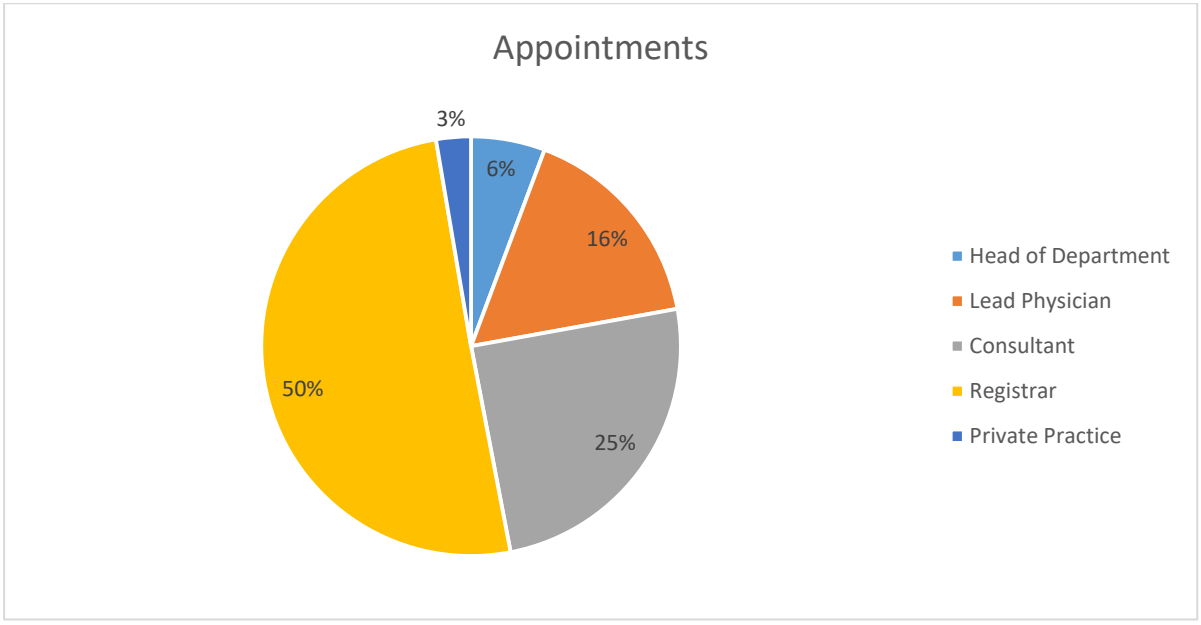

Figure 38 – Appointments

A total of 306 participants (96.2%) indicated the size of institution in which they are employed. The majority of participants work at a cantonal hospital. Approximately one-third of the participants work at a university hospital, and only a minority work at regional hospitals or in private practice.

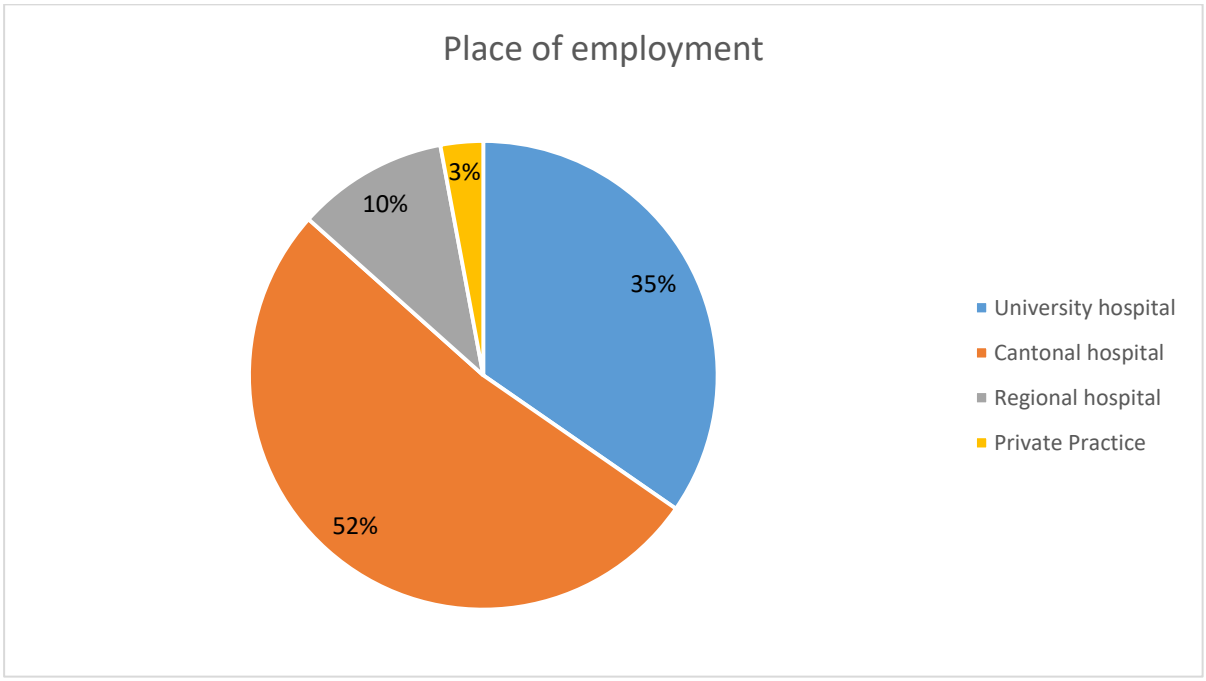

Figure 39 – Place of employment

7.8.3 Involvement of Diagnostic or Therapy of IE

In total, 290 participants (91.2%) indicated whether or not they are involved in the diagnostics or therapy of IE in clinical practice; 90% of the responders answered this question with a 'yes'.

7.8.4 Specialisation

A total of 286 participants (90%) indicated their specialisation. The vast majority (176 participants, 61.5%) of participants completed training in general internal medicine. As noted previously, of these 176 participants, 91 (31.8% of total participants) completed training in two specialities, and 37 (12.9%) are currently in training for a second speciality. Fifty-one participants (17.8%) completed training in infectious diseases and 35 (12.2%) in cardiology. Only 19 participants (6.6%) completed a different type of training (seven in nephrology, four in endocrinology/diabetology, two in anaesthesiology, two in intensive care, two in oncology, one in rheumatology, one in angiology). In most cases, this was in addition to training in general internal medicine.

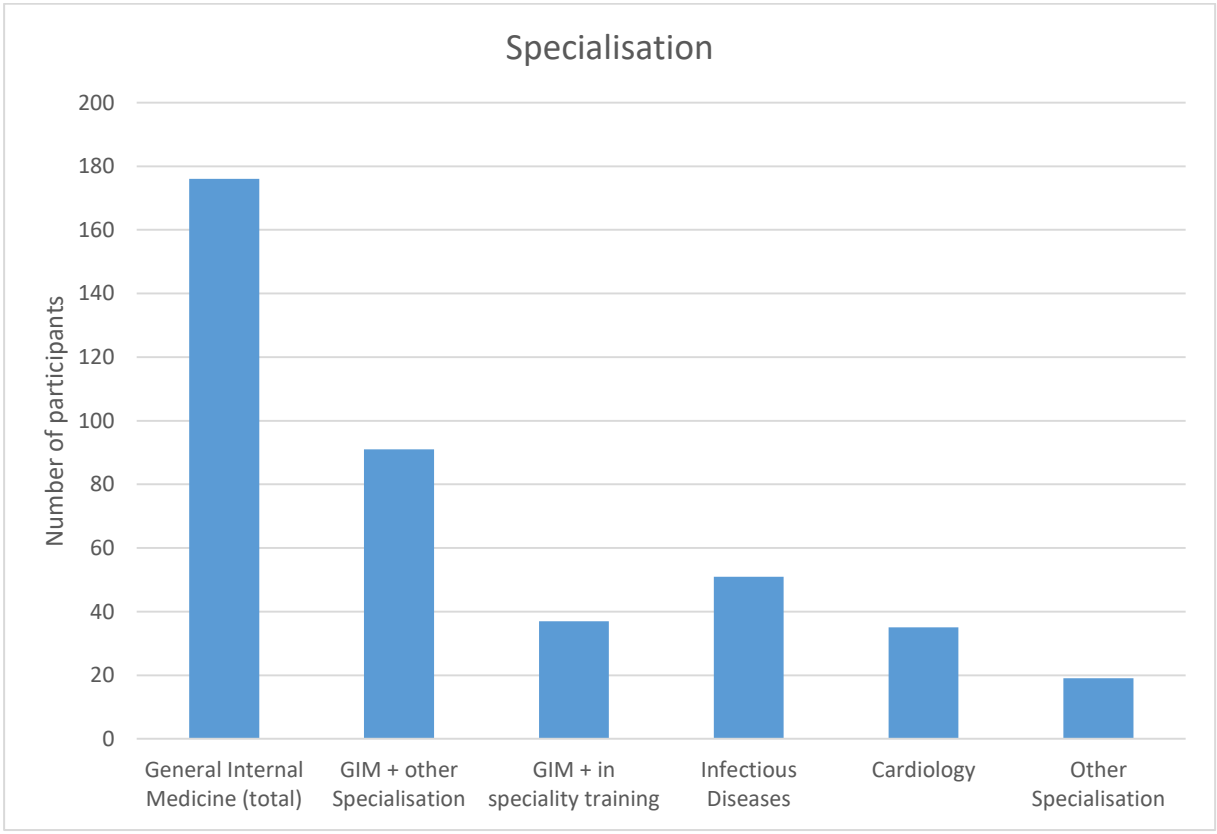

Figure 40 – Specialisation of participants

GIM: general internal medicine

7.8.5 QUESTION 1

Question 1 was a knowledge question. Physicians were asked what – according to their knowledge – a predisposing heart condition is.

A total of 306 participants (96.2%) answered this question, of which 296 answers (96.7%) were reasonable. In 10 questionnaires, the answers could not be interpreted by the study team. The total is >100% because multiple answers were possible. To calculate the percentage, we used the number of participants who answered this question.

Forty-five participants (14.7%) indicated at least one wrong answer. A wrong answer was defined as an answer that did not include heart conditions (e.g. IVDU, immunosuppression, in-dwelling catheter), as we specifically asked for heart conditions. The rate of wrong answers for each specialty was not different (internal medicine, 14.2%; cardiology, 15.7%; infectious diseases, 14.3%; other, 15.8%). In addition, the same analysis was conducted for the appointments of the participants, with no difference in the rate of wrong answers (registrars, 15.3%; consultants, 13.5%; lead physicians, 14.3%; head of departments, 11.8%). There was a difference in analysis for years of clinical experience: 30.7% wrong answers for 1–2 years of clinical experience, 11.7% for 3–5 years of clinical experience, and 14.3% for >5 years of clinical experience.

Answer (More Than 1 Possible)	Number of Participants	%
IVDU	33	10.8
Prior IE	99	32.4
AI	31	10.1
AS	35	11.4
BAV	39	12.7
MI	39	12.7
MS	27	8.8
MVP	37	12.1
PI	20	6.5
PS	14	4.6
TI	25	8.2
TS	17	5.6
Foreign body material (devices, pacemakers, valve replacements…)	205	67.0
Previous heart surgery (without foreign body material, or not specified)	12	3.9
Heart transplant	9	2.9
Defect leading to significant turbulence	8	2.6
Dilatative cardiomyopathy	1	0.3
Obstructive cardiomyopathy	4	1.3
Heart failure	10	3.3
Vitium (not specified)	50	16.3
GUCH	58	19.0
Shunt	48	15.7
Valve vitium	80	26.1
Cyanotic heart defect	25	8.2
Rheumatic heart disease	28	9.2
Degenerative valve disease	16	5.2
Immunosuppression	10	3.3
In-dwelling catheter	2	0.7

Table 18 – Answers to Question 1

AI: aortic valve insufficiency/regurgitation; AS: aortic valve stenosis; BAV: bicuspid aortic valve; IE: infective endocarditis; GUCH: grown-up with congenital heart disease; IVDU: intravenous drug user; MI: mitral valve insufficiency/regurgitation; MS: mitral valve stenosis; MVP: mitral valve prolapse; PI: pulmonary valve insufficiency/regurgitation; PS: pulmonary valve stenosis; TI: tricuspid valve insufficiency/regurgitation; TS: tricuspid valve stenosis

	Wrong Answers	**Participants in Group**	**%**
Internal medicine	25	176	14.2
Cardiology	8	51	15.7
Infectious diseases	5	35	14.3
Other	3	19	15.8

Table 19 – Wrong answers to Question 1 analysed by speciality

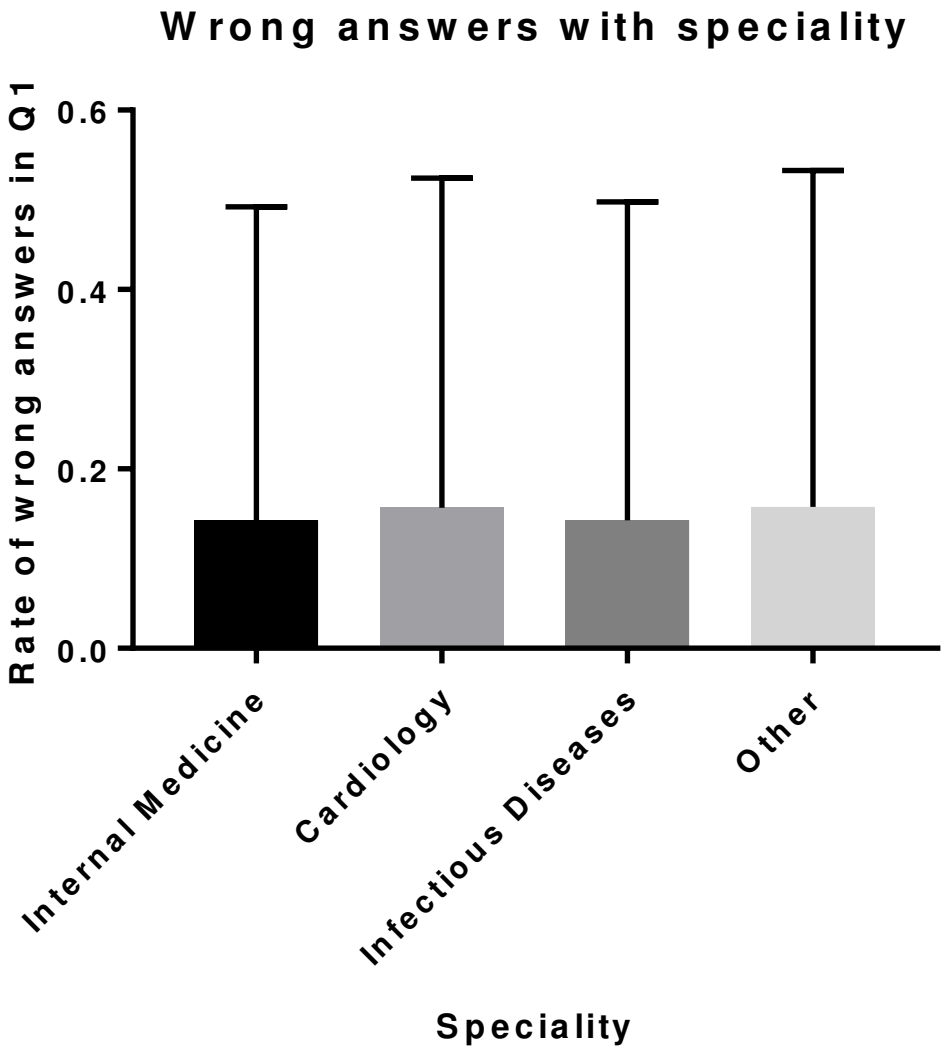

Figure 41 – Statistical analysis of speciality compared with rate of wrong answers in Q1, ANOVA

ANOVA: analysis of variance; Q1: Question 1

	Wrong Answers	Participants in Group	%
Registrar	23	150	15.3
Consultant	10	74	13.5
Lead physician	7	49	14.3
Head of department	2	17	11.8

Table 20 – Wrong answers to Question 1 analysed by appointment

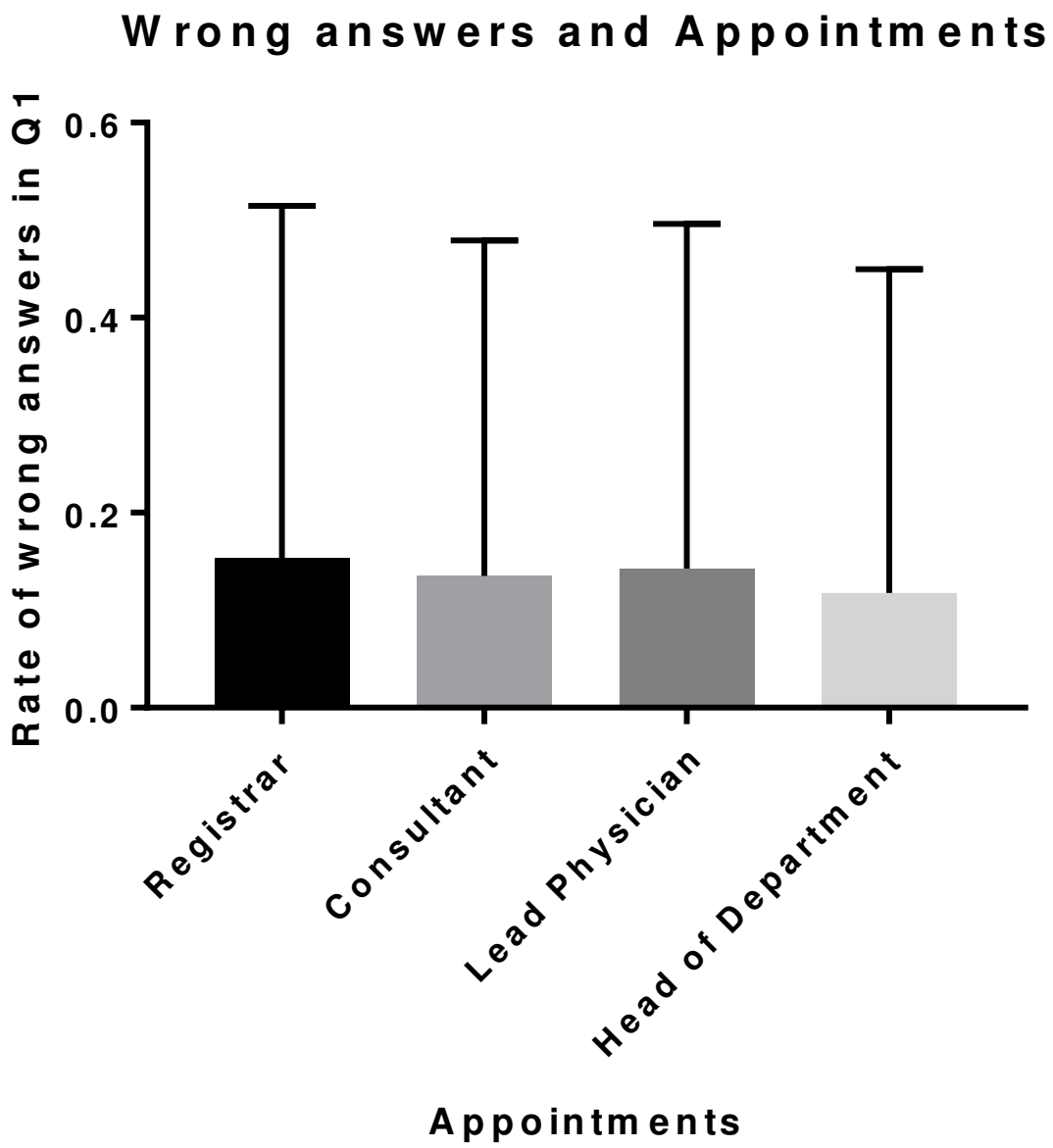

Figure 42 – Statistical analysis of rate of wrong answers in Q1 and appointments of participants, ANOVA

ANOVA: analysis of variance; Q1: Question 1

	Wrong Answers	Participants in Group	%
1–2 years	4	13	30.8
3–5 years	7	60	11.7
>5 years	34	237	14.3

Table 21 – Question 1 wrong answers analysed by years of clinical experience

Figure 43 – Statistical analysis of rate of wrong answers and years of clinical experience, t-test

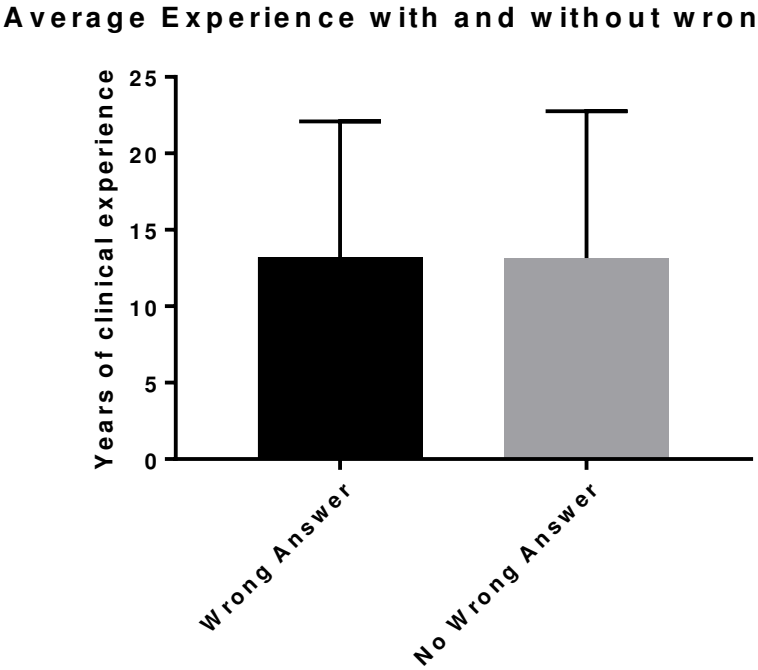

Figure 44 – Statistical analysis of average years of clinical experience of participants with and without wrong answers, t-test

7.8.6 QUESTION 2

Question 2 was another knowledge question. We asked whether predisposing heart conditions for native valve IE are specifically defined in either European or American guidelines for IE.

In total, 312 participants (98.1%) answered this question. Fifty-four participants (17.3%) answered yes, 83 participants (26.6%) answered no, and 175 participants (56.1%) indicated that they do not know the answer.

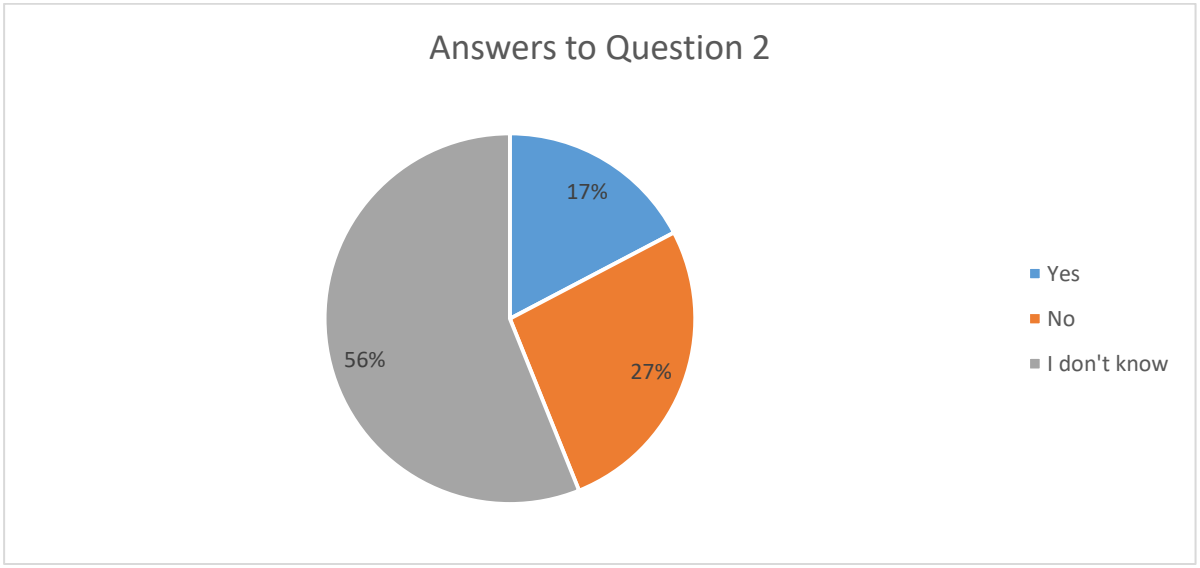

Figure 45 – Answers to Question 2

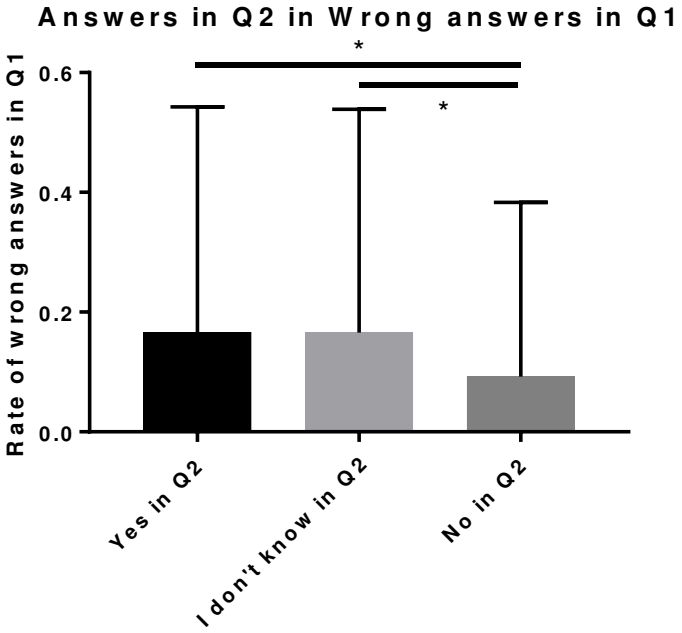

Figure 46 – Statistical analysis of answers to Q2 compared with participants with wrong answers to Q1, t-test

Q1: Question 1; Q2: Question 2

7.8.7 QUESTION 3

A total of 297 (93.4%) participants answered this question. The total is >100% because multiple answers were possible. To calculate the percentage, we used the number of participants who answered this question. As this question asked for the opinion of participants, no answers could be defined as wrong.

Answer	Number of Participants	%
IVDU	7	2.4
Prior IE	68	22.9
AI	61	20.5
AS	92	31.0
BAV	86	29.0
MVP	96	32.3
MI	96	32.3
MS	79	26.6
TI	53	17.8
TS	43	14.5
PI	40	13.5
PS	40	13.5
Prior myocardial infarction, coronary heart disease	4	1.3
Foreign body material (valve replacement, devices, pacemakers…)	51	17.2
Heart transplant	5	1.7
Heart failure	7	2.4
Atrial fibrillation, other arrhythmias	2	0.7
Hypertrophic cardiomyopathy	1	0.3
Vitium (not specified)	23	7.7
Valve vitium	35	11.8
Shunt	39	13.1
Cyanotic heart disease	13	4.4
Rheumatic heart disease	37	12.5
GUCH	26	8.8
HOCM	4	1.3
DCM	3	1.0
Thrombus	2	0.7
Tumour	1	0.3
Endothelial damage	3	1.0
Valve sclerosis/calcification	45	15.2
Cardiac surgery (without foreign body material)	13	4.4
Paravalvular leakage	1	0.3
Dental disease	1	0.3
Cardiac disease causing significant turbulences	8	2.7
Low flow	1	0.3
Immunosuppression (also diabetes mellitus, HIV…)	2	0.7
Chronic inflammation	11	3.7
Kidney failure, hyperparathyroidism	1	0.3

Table 22 – Answers to Question 3

AI: aortic valve insufficiency/regurgitation; AS: aortic valve stenosis; BAV: bicuspid aortic valve; DCM: dilated cardiomyopathy; IE: infective endocarditis; GUCH: grown-up with congenital heart disease; HOCM: hypertrophic obstructive cardiomyopathy; IVDU: intravenous drug user; MI: mitral valve insufficiency/regurgitation; MS: mitral valve stenosis; MVP: mitral valve prolapse; PI: pulmonary valve insufficiency/regurgitation; PS: pulmonary valve stenosis; TI: tricuspid valve insufficiency/regurgitation; TS: tricuspid valve stenosis

The cardiac conditions specified in both Question 1 and Question 3 did not differ significantly, as shown in Table 23.

Condition	Knowledge Question 1 (% of Participants)	Opinion Question 3 (% of Participants)
Aortic valve insufficiency	10.1	20.5
Aortic valve stenosis	11.4	31.0
Arrhythmias	0	0.7
Bicuspid aortic valve	12.7	29.0
Cardiac surgery (without foreign body material)	3.9	4.4
Cyanotic heart disease	8.2	4.4
DCM	0.3	1.0
Degenerative valve disease	5.2	0
Endothelial damage	0	1.0
Foreign body material	67	17.2
GUCH	19.0	8.8
Heart failure	3.3	2.4
Heart transplant	2.9	1.7
Hypertrophic cardiomyopathy	0	0.3
HOCM	1.3	8.8
Low flow	0	0.3
Mitral valve insufficiency	12.7	32.3
Mitral valve prolapse	12.1	32.3
Mitral valve stenosis	8.8	26.6
Paravalvular leakage	0	0.3
Prior infective endocarditis	32.4	22.9
Prior myocardial infarction/coronary heart disease	0	1.3
Pulmonary valve insufficiency	6.5	13.5
Pulmonary valve stenosis	4.6	13.5
Rheumatic heart disease	9.2	12.5
Significant turbulence	2.6	2.7
Shunt	15.7	13.1
Thrombus	0	0.7
Tricuspid valve insufficiency	8.2	17.8
Tricuspid valve stenosis	5.6	14.5
Tumour	0	0.3
Valvular vitium	26.1	11.8
Vitium (not specified)	16.3	7.7

Table 23 – Comparison between conditions named in answers to Question 1 and Question 3

DCM: dilated cardiomyopathy; GUCH: grown-up with congenital heart disease; HOCM: hypertrophic obstructive cardiomyopathy

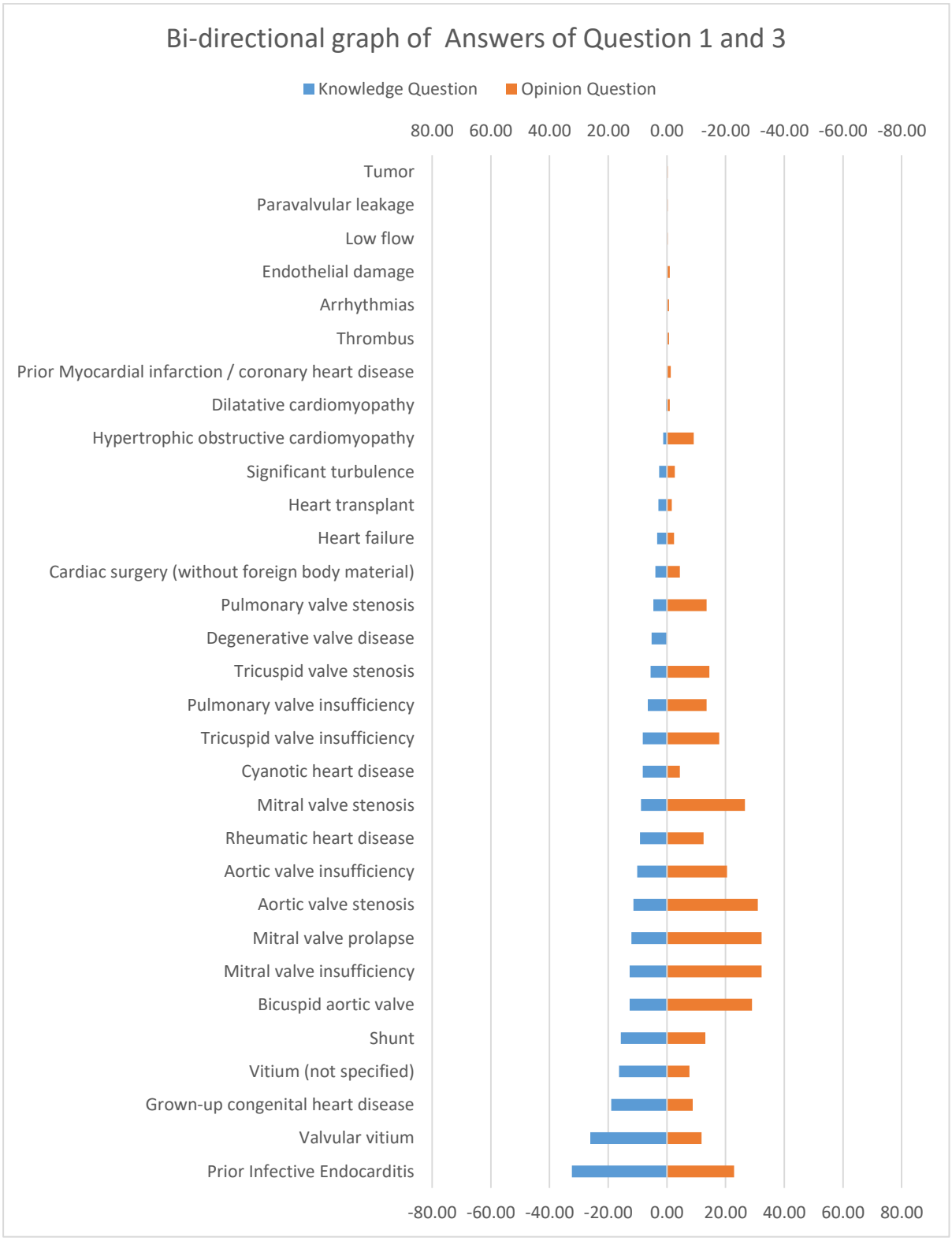

Figure 47 – Bidirectional graph comparing answers to Question 1 with answers to Question 3

7.8.8 QUESTION 4

Question 4 asked participants to state the expected outcome if the study of Clemens et al.[20] were repeated today. Clemens et al. conducted a case-control study with 51 patients with IE and 153 matched controls without IE. They stated that patients with MVP had a significantly higher risk of developing IE compared with patients without MVP (odds ratio 8.2, 95% CI 2.4–28.4).

A total of 308 participants (96.9%) answered this question. The total is >100% because multiple answers were possible. To calculate the percentage, we used the number of participants who answered this question.

Answer 1 stated that participants would expect the repeat study to yield similar results.

Answer 2 stated that participants would expect similar results, but with a lower odds ratio.

Answer 3 stated that participants would not expect similar results, as the criteria in use today for MVP are different from those used in 1982.

Answer 4 stated that participants would not expect similar results, as the echocardiographic technique used today is better than it was in 1982, and thus MVP was overdiagnosed in 1982.

Answer 5 stated that participants would not expect similar results, as results from almost all cardiologic studies that are older than 30 years cannot be applied today.

Answer	Number of Participants	%
1	51	16.0%
2	81	25.5%
3	92	28.9%
4	117	36.8%
5	35	11.0%

Table 24 – Answers to Question 4

Twelve participants (3.9%) chose contradictory answers (e.g. Answer 1 and Answer 3).

In the analysis for speciality, appointment, and years of clinical experience, the number of answers can be higher than the number of participants, as several answers were possible.

	Yes: Answers 1 or 2 (%)	No: Answers 3, 4, or 5 (%)	Contradiction (%)
Internal medicine	60 (34.1%)	154 (87.5%)	19 (10.8%)
Cardiology	14 (27.5%)	53 (103.9%)	4 (7.8%)
Infectious diseases	20 (57.1%)	25 (71.4%)	7 (20.0%)
Other	5 (26.3%)	18 (94.7%)	0 (0.0%)

Table 25 – Answers to Question 4 analysed by speciality

	Yes: Answers 1 or 2 (%)	No: Answers 3, 4, or 5 (%)	Contradiction (%)
Registrar	73 (48.7%)	95 (63.3%)	30 (20.0%)
Consultant	30 (40.5%)	61 (82.4%)	11 (14.9%)
Lead physician	17 (34.7%)	44 (89.8%)	6 (12.2%)
Head of department	4 (23.5%)	18 (105.9%)	1 (5.9%)

Table 26 – Answers to Question 4 analysed by appointment

	Yes: Answers 1 or 2 (%)	No: Answers 3, 4, or 5 (%)	Contradiction (%)
1–2 years of experience	9 (69.2%)	9 (69.2%)	5 (38.5%)
3–5 years of experience	30 (50.0%)	32 (53.3%)	12 (20.0%)
>5 years of experience	93 (39.2%)	199 (84.0%)	34 (14.3%)

Table 27 – Answers to Question 4 analysed by years of clinical experience

8 DISCUSSION

In a study by Rognon et al.,[74] 76% of patients with IE had a predisposing heart condition as a minor criterion for diagnosing IE. The authors stated that in the absence of the minor criterion, 27% of definite IE would be relegated to lower diagnostic categories. In a study by Durante-Mangoni et al.[161], the criterion 'predisposing native cardiac condition' was fulfilled in 29.7% of younger IE patients and in 34.9% of elderly patients. In a study by Habib et al.,[279] the criterion 'predisposition, heart disease' was fulfilled in 71% of patients. These data underline that it is commonly accepted that certain heart valve pathologies predispose for IE. In clinical practice, however, it is unclear which of the possible heart pathologies pose a significant risk for developing an IE, and if they do, to what extent.

Our general objective was to narrow the definition of predisposing heart condition in native valves for the diagnosis of IE. Therefore, we divided the objective into three specific aims: first, to review the literature and the evidence on specific heart conditions reported to be a risk factor for IE; second, to align the findings from the first aim with the imaging technique available at that time and to theoretically compare, via extrapolation, the results with imaging from today's perspectives and current definitions of a specific heart condition (i.e. valvular disease); and third, to evaluate the knowledge and opinion of clinicians about the term predisposing heart condition.

The vast majority of the studies were descriptive. Only a few studies investigated a valve pathology as a risk factor for IE via analytical statistics. Moreover, three-quarters of all included studies involved patients who presented with IE prior to the publication of the modified Duke criteria. On the basis of our analyses, we can categorise the publications – irrespective of quality – into three groups. The first group included risk factors with a large number of publications. Studies belonging to this group focussed on (i) MVP (111 publications), (ii) prior IE (91 publications), and (iii) BAV (78 publications). In contrast, there was a group with few publications. Studies belonging to this group included (i) patients with MS (23 publications), (ii) pathologies involving the pulmonary valve (18 publications), and (iii) pathologies involving the tricuspid valve (nine publications). Between these two groups, we allocated a third group as having a medium number of number of publications. This group included patients with (i) AS (46 publications), (ii) MI (41 publications), and (iii) AI (39 publications).

8.1 Group 1 – Predisposing Heart Conditions with a High Number of Publications

8.1.1 MVP

We identified six studies showing that a history of MVP was associated with a higher risk of IE. One study was excluded because of small patient numbers.[224] Two studies reported an odds ratio of approximately 8,[20,226] one an odds ratio of 3,[225] another an odds ratio of 6.7,[223] and another an odds ratio of 19.2.[9] However, all of these analyses were performed in studies prior to the release of the modified Duke criteria (published 2000). Similarly, 81.2% of the 110 descriptive studies included patients after the publication of the modified Duke criteria. Moreover, our review on the evolution of imaging methods in parallel with the published studies indicates that the diagnostic accuracy of MVP is uncertain in a large proportion of these studies. For many years, MVP was diagnosed via auscultation. In 1998, ACC stated that there was no consensus in on the 2D echocardiographic criteria for MVP.[176] On the basis of these arguments, the risk of developing IE and the prevalence of patients with MVP among those with IE cannot be quantified from today's perspective. Given this line of reasoning, the meaning of the proportion of patients with MVP who developed IE (mean 8.5%, median 7.7%, IQR 4.4%–11.4%) is unclear.

8.1.2 Prior IE

The evolution of imaging methods did not – in our view – influence these results. Among the descriptive studies, 24.7% included patients after the publication of the modified Duke criteria. However, in earlier studies, the diagnosis was made on the basis of other defined criteria or via autopsy. Although we cannot estimate whether the variable prior IE was over- or underestimated in these studies, there were no considerable reasons to mistrust the diagnosis. Two studies showed an odds ratio of approximately 2.5[48,49] for developing IE when patients had previously experienced an episode of IE. The mean proportion of patients with IE plus a history of previous IE was 8.3% (median 7.1%, IQR 4.9%–10.2%). These results did not alter significantly when we compared studies before and after 2001. These numbers indicate that every tenth to twentieth patient with a history of IE will develop a second episode of IE.

8.1.3 Bicuspid Aortic Valve

We identified one analytical study showing that a history of BAV was associated with a higher risk of IE, with a hazard ratio of 6.3.[141] In the 77 descriptive studies, a median of 5.6% (before 2001, 7.0%; after 2001, 5.0%) of patients with IE had BAV as an underlying condition. Of these 77 studies, 20 (26%) included patients after the publication of the modified Duke criteria. Nonetheless, given the

fact that the presence of BAV could be imagined in the mid-70s, we judged the influence of imaging over time as minor.

8.2 Group 2 – Predisposing Heart Conditions with a Low Number of Publications

8.2.1 Mitral Valve Stenosis

MS is often associated with rheumatic heart disease, which by itself has been suggested as a risk factor for developing IE. The prevalence of rheumatic fever has been constantly decreasing in the Western world. The mean prevalence of patients with MS and IE in publications prior to 2001 was 6.4% (median 5.3%, IQR 3.2%–7.6%). After 2001, the IQR dropped to 0.7%–2.5%. Similarly, the dot plot graph indicates that with the increasing sample size number in the corresponding studies with definitions in accordance with the modified Duke criteria, the prevalence of IE in patients with MS is ≤1%. Although it appears meaningful that turbulence caused by MS predisposes to IE, it is difficult to say whether MS itself poses an increased risk or whether rheumatic fever is a surrogate marker. Our literature review on the evolution of imaging methods did not provide important arguments that the diagnosis of MS was underdiagnosed. More likely, MS was overdiagnosed before 1998 because of the diagnostic criteria for rheumatic fever. From today's perspective, patients with diagnosed MS frequently experience valve replacement, and hence, MS per se cannot be quantified as a risk for developing IE.

8.2.2 Pulmonary Valve

We identified one study analysing the risk of developing IE in patients with congenital PS, reporting a hazard ratio of 1.1.[141] No studies of PI or other aetiologies of PS were identified in the literature review. From the 17 descriptive studies, a median of 1% of patients with IE had PS or PI. Only four studies were published after the modified Duke criteria, and among those, the median of patients with PS and IE was 0.3% (mean 0.3%, IQR 0.2%–0.3%). Similarly, the dot plot graph indicates a very low prevalence throughout all studies. PS is most important when considering congenital heart disease. The clinical role in adults, however, is less important and may result from rare causes, such as in patients with carcinoid plaques,[278] or in the modern era, in patients who had heart surgery in their childhood. As definitions of PI/PS were not added to the guidelines until 2006,[5] it is improbable that this severely influenced reporting in our case, as most studies reported here were published before 2006.

8.2.3 Tricuspid Valve

No studies reporting an odds ratio for patients with TI or TS for developing IE were identified. Of the nine studies with descriptive reporting, a median of 5% of patients with IE had TI or TS as an underlying condition.

Of these nine studies, three included only patients after the publication of the modified Duke criteria. Echocardiographic criteria were not included in the guidelines until 2006[272] and were made more precise in 2014.[2] Moreover, the dot plot graph indicates that some of these studies have a publication bias. As only a small number of studies were published on TI/TS and IE, it is difficult to speculate on the relevance.

8.3 Group 3 – Predisposing Heart Conditions with a Medium Number of Publications

This group is – within the aims of our thesis – the most difficult for the following reasons. First, in comparison to group 1, the number of publications in this group is below 50, and hence, there is less postulated evidence. Second, AS, MI, and AI are among the most common valve pathologies in our population. This is in particular true for the Western world with its growing number of elderly people. In the proportion analyses, this makes the denominator difficult to estimate. Third, with the evolution of imaging, these pathologies haven been classified differently over time. Thus, what might have been a risk factor in previous studies is no longer one from today's perspective, because a valve pathology is classified as mild, moderate, or severe, and each category does not fulfil the statistical criteria.

8.3.1 Aortic Stenosis

We identified only one study showing that a history of (congenital) AS was associated with a higher risk of IE, with a hazard ratio of 4.9.[141] Of the 45 studies with descriptive analyses, 11 (24.4%) included patients in the study after the publication of the modified Duke criteria. The differentiation between mild, moderate, and severe AS was described first in 1989, although it was only after 1998 that the definitions of mild, moderate, and severe AS were published in guidelines. The observation that (i) three-quarters of the studies included patients prior to 2001, (ii) the mean and median proportion of patients with AS and IE was lower in studies published after 2001 (5.2% and 4.5%, respectively) than in studies published before 2001 (8% and 7%, respectively), and (iii) the dot plot demonstrates a prevalence of less than 5% in newer studies with large sample sizes indicates that the

relevance of mild or moderate AS as a risk factor for IE is unknown. This is in line with the study of Gersony et al.[142] in which they postulated that only severe AS is related to the occurrence of IE.

8.3.2 Mitral Valve Insufficiency

In the literature review, no studies reporting analytical statistics for patients with MI for developing IE could be identified. Forty-one studies were identified that published descriptive statistics on the proportion of patients with MI in newly diagnosed IE cases. Of these studies, nine (22%) included patients in the study after the publication of the modified Duke criteria. The proportion of patients with IE and MI had a wide distribution of results, i.e. the overall IQR was 5.2%–28.6%, was 5%–25.7% in publications prior to 2001, and was 9.6%–37.8% in publications after 2001. The dot plot also indicates that the literature research included studies with a publication bias. This may be because the research question is difficult to answer in this constellation. For example, some studies may represent that their patients developed MI because of IE and not that MI was a risk factor for developing IE. Finally, the definitions of the graduation of MI were implemented rather late, namely in the 2006 guidelines,[5] again after the recommendations by ASE.[192] Taken together, these findings indicate that the current literature research result does not allow any conclusion regarding MI as risk factor for IE. Refining of the included studies may therefore be more helpful (see Outlook section below [8.6]).

8.3.3 Aortic Valve Insufficiency

In our literature review, no studies with analytical statistics for patients with AI and their risk of developing IE could be identified. Thirty-nine studies were identified that published descriptive statistics on the proportion of patients with a history of AI in newly diagnosed IE cases. Of these studies, eight (20.5%) included patients in the study after the publication of the modified Duke criteria. Before 1998, visualisation by cineangiography and eyeball guessing of the regurgitant volume was common. In 2003, with recommendations by ASE,[192] and later in 2006 with implementations in the AHA guidelines,[5] the echo criteria were published. Given the fact that 80% of publications addressed the AI risk factor prior to the presentation of the modified Duke criteria, overestimation of AI as a predisposing condition is possible. The difficulty in assessing AI as a risk factor is reflected by the wide range (IQR 2.4%–25%) in the number of patients with AI and IE in publications after 2001 and the wide distribution in the dot plot graph comparing sample size and prevalence of IE in patients with AI. With the current data, AI as a risk factor in developing IE cannot be quantified.

8.4 How Do We Currently Interpret the Duke Minor Criterion Predisposing Heart Condition in Native Valves?

Our survey shows that in clinical practice, there is uncertainty regarding what is considered a Duke minor criterion predisposing heart condition in a native valve. The range of answers regarding the nature of a predisposing heart condition was very broad. The answers regarding what participants believed to be true (knowledge question) and what they felt should be true (opinion question) were not similar on many of the questionnaires. On the one hand, these results may underline the difficulty in diagnosing IE in clinical practice, and on the other, they may point towards uncertainty in how to interpret and apply the Duke minor criterion of a predisposing heart condition. We found an association only between the wrong answers (very narrowly defined) in clinicians with less than 3 years of clinical experience. Two-thirds of the participants were convinced that in previous years, the diagnosis of MVP was overestimated. If this is true, a certain proportion of patients was falsely postulated to be at risk for IE. This again may have influenced the statistical risk stratification. A repetition of this study with current diagnostic methods may help to answer this question. Our survey does not provide final results other than to show that there is a trend for uncertainty regarding what is considered a Duke minor criterion predisposing heart condition in a native valve.

8.5 LIMITATIONS

The thesis results have limitations. First, the literature review includes studies with considerable heterogeneity. In many articles, the underlying heart disease was not specified in detail. It was often reported by aetiology (rheumatic, congenital, degenerative), but not categorised as mild, moderate, or severe. The means by which the diagnosis of the predisposing cardiac conditions was made remain unreported in most studies. In addition, in some studies, it was unclear – despite detailed full text information – as to whether the reported cardiac condition was present before IE, or whether it was caused by IE itself (e.g. valve insufficiency). In a significant number of studies, the corresponding valve pathology in a population was not reported (i.e. patients with valve pathology but without IE). Thus, it is possible that the reported number of predisposing heart conditions overestimates the true prevalence in IE. By using a dot plot graph that associates sample size with proportion of IE, we aimed to identify studies with publication bias (e.g. shown for MI). Finally, the diagnostic criteria varied among the studies. Some articles used the original Duke criteria even after the modified criteria were published. We tried to counterbalance this observation by categorising studies prior to 2001 and after 2001. We thereby focused on the years in which the patients were included in each study and not on the publication year of the corresponding study.

Second, our historical view on the evolution of imaging methods is based on the published literature. The extrapolation about whether each study could use imaging methods that were modern in their time is theoretical.

Third, the survey has a selection bias of participants because only physicians present at morning meetings on the date of investigation filled out the questionnaire. Although the questionnaire was tested on several occasions, it was not validated prior to the study.

8.6 OUTLOOK

Our systematic review of the literature is the basis for further analyses, in particular meta-analyses. In a first step, we will address the limitations mentioned above and exclude studies that do not address the research questions properly. Further tests are necessary to look for publication bias (e.g. Egger test). The heterogeneity can be addressed with a plot of precision versus response proportion (e.g. Freeman-Tukey, Begg funnel plot). By doing this, it will become apparent which studies with a smaller sample size or precision will have a larger random error and thus a larger spread when graphed. These steps are necessary for every variable mentioned in this thesis to obtain a proper data set. We can thereby process our current systematic literature review into a second meta-analysis. Finally, we may also proceed with a sensitivity analyses to estimate the proportion risk of IE for each valve disease. With the aid of mathematical models a more narrow definition of the term predisposing heart condition can be targeted.

8.7 Concluding Remarks and Potential Consequences for Clinical Practice

Our work demonstrates that there is uncertainty about what is considered a predisposing heart condition for the diagnosis of IE. This uncertainty is found even with an extensive literature review. The vast majority of studies contained only descriptive statistics and included patients in the study prior to the publication of the modified Duke criteria. The highest number of articles in the literature were related to MVP, a prior episode of IE, and BAV. Among these three variables, MVP is most likely affected by the evolution of imaging methods, in particular because for many years, diagnosis of this valve pathology was made via auscultation. The uncertainty was also found after analysing the responses of 318 physicians in a questionnaire.

This diagnostic uncertainty may lead to overdiagnosis of IE in patients with positive results of blood cultures (e.g. non-staphylococcal bacteraemia) but inconclusive imaging results. Nonetheless, in the early phase of disease and with suspicion of IE, it may be prudent to overdiagnose disease and perform echocardiography. In the longer course of the disease, however, overtreatment of IE contributes to the development of organism resistance in the microbiome and is associated with adverse events from antimicrobial agents. An imprecise Duke minor criterion is, in our view, not helpful in decision-making for or against the final diagnosis of IE. In our view, it is reasonable to encounter anatomical variants that cause significant turbulence and may be risk factors when IE is suspected at first clinical presentation. However, over a 2-week period, the clinical course, the microbiological criteria, and repeated imaging with modern techniques should allow confirmation or rejection of the definite diagnosis of IE in most cases, irrespective of the presence of valve disease.

9 ACKNOWLEDGMENTS

We are indebted to our supervisor, Parham Sendi, for his invaluable comments and ongoing support during the course of this dissertation.

Sven Trelle, Stephan Zbinden, and Andrew Atkinson were of great help with designing the questionnaire, the cardiological problems, and the meta-analysis, respectively.

Barbara Every, ELS, of BioMedical Editor, St. Albert, Alberta, Canada, provided English language editing.

And last – but not least – we thank our families and friends for their support and patience during the time we were working on this thesis.

10 INDEX OF FIGURES

11 INDEX OF TABLES

12 LITERATURE

1. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2000;30:633-8.

2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:e57-185.

3. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. The American journal of medicine 1994;96:200-9.

4. Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. Annals of internal medicine 1981;94:505-18.

5. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006;114:e84-231.

6. Bonow ROM, D.L.; Zipes, D.P.; Libby, P. Braunwald's Heart Disease: A textbook of Cardiovascular medicine 9th edition: Elsevier; 2012.

7. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. II. Antecedent procedures and use of prophylaxis. Archives of internal medicine 1992;152:1869-73.

8. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. I. Patient characteristics. Archives of internal medicine 1992;152:1863-8.

9. Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. Annals of internal medicine 1998;129:761-9.

10. Moreillon P, Que YA. Infective endocarditis. Lancet (London, England) 2004;363:139-49.

11. Patti JM, Hook M. Microbial adhesins recognizing extracellular matrix macromolecules. Current opinion in cell biology 1994;6:752-8.

12. Osler W. The Gulstonian Lectures, on Malignant Endocarditis. British medical journal 1885;1:577-9.

13. Millar BC, Moore JE. Emerging issues in infective endocarditis. Emerging infectious diseases 2004;10:1110-6.

14. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. European heart journal 2009;30:2369-413.

15. Dajani AS, Bisno AL, Chung KJ, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. Jama 1990;264:2919-22.

16. Morris CD, Reller MD, Menashe VD. Thirty-year incidence of infective endocarditis after surgery for congenital heart defect. Jama 1998;279:599-603.

17. PREVENTION of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Pediatrics 1955;15:642-6.

18. Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2006;42:e102-7.

19. Cherubin CE, Neu HC. Infective endocarditis at the Presbyterian Hospital in New York City from 1938-1967. The American journal of medicine 1971;51:83-96.

20. Clemens JD, Horwitz RI, Jaffe CC, Feinstein AR, Stanton BF. A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. The New England journal of medicine 1982;307:776-81.

21. Beton DC, Brear SG, Edwards JD, Leonard JC. Mitral valve prolapse: an assessment of clinical features, associated conditions and prognosis. The Quarterly journal of medicine 1983;52:150-64.

22. McKinsey DS, Ratts TE, Bisno AL. Underlying cardiac lesions in adults with infective endocarditis. The changing spectrum. The American journal of medicine 1987;82:681-8.

23. Weinberger I, Rotenberg Z, Zacharovitch D, Fuchs J, Davidson E, Agmon J. Native valve infective endocarditis in the 1970s versus the 1980s: underlying cardiac lesions and infecting organisms. Clinical cardiology 1990;13:94-8.

24. Curie J. CP. Développement, par pression, de l'électricité polaire dans les cristaux hémièdres à faces inclinées. Comptes Rendus de l'Académie des Sciences 1880;91:294-5.

25. Dussik KT. On the possibility of using ultrasound waves as a diagnostic aid. Neurol Psychiat 1942;174:153-68.

26. Edler I, Hertz CH. The use of ultrasonic reflectoscope for the continuous recording of the movements of heart walls. 1954. Clinical physiology and functional imaging 2004;24:118-36.

27. Feigenbaum H, Waldhausen JA, Hyde LP. Ultrasound Diagnosis of Pericardial Effusion. Jama 1965;191:711-4.

28. Feigenbaum H, Popp RL, Chip JN, Haine CL. Left ventricular wall thickness measured by ultrasound. Archives of internal medicine 1968;121:391-5.

29. Gramiak R, Waag RC, Simon W. Cine ultrasound cardiography. Radiology 1973;107:175-80.

30. Bom N, Lancee CT, van Zwieten G, Kloster FE, Roelandt J. Multiscan echocardiography. I. Technical description. Circulation 1973;48:1066-74.

31. Johnson SL, Baker DW, Lute RA, Dodge HT. Doppler echocardiography. The localization of cardiac murmurs. Circulation 1973;48:810-22.

32. Griffith JM, Henry WL. A sector scanner for real time two-dimensional echocardiography. Circulation 1974;49:1147-52.

33. Dekker DL, Piziali RL, Dong E, Jr. A system for ultrasonically imaging the human heart in three dimensions. Computers and biomedical research, an international journal 1974;7:544-53.

34. Eggleton RC, Feigenbaum H, Johnston KW, Weyman AE, Dillon JC, Chang S. Visualization of Cardiac Dynamics with Real Time B-Mode Ultrasonic Scanner. In: White D, ed. Ultrasound in Medicine: Volume 1 Proceedings of the 19th Annual Meeting of the American Institute of Ultrasound in Medicine. Boston, MA: Springer US; 1975:385-93.

35. Frazin L, Talano JV, Stephanides L, Loeb HS, Kopel L, Gunnar RM. Esophageal echocardiography. Circulation 1976;54:102-8.

36. Holen J, Simonsen S. Determination of pressure gradient in mitral stenosis with Doppler echocardiography. British heart journal 1979;41:529-35.

37. Hatle L, Angelsen BA, Tromsdal A. Non-invasive assessment of aortic stenosis by Doppler ultrasound. British heart journal 1980;43:284-92.

38. Hisanaga K, Hisanaga A, Nagata K, Ichie Y. Transesophageal cross-sectional echocardiography. American heart journal 1980;100:605-9.

39. Hanrath P, Kremer P, Langenstein BA, Matsumoto M, Bleifeld W. [Transesophageal echocardiography. A new method for dynamic ventricle function analysis]. Deutsche medizinische Wochenschrift (1946) 1981;106:523-5.

40. Kitabatake A, Inoue M, Asao M, et al. Transmitral blood flow reflecting diastolic behavior of the left ventricle in health and disease--a study by pulsed Doppler technique. Japanese circulation journal 1982;46:92-102.

41. Schlüter MH, P. Transesophageal echocardiography: potential advantages and initial clinical results. Practical Cardiol 1983;9:149-71.

42. Pandian NG, Nanda NC, Schwartz SL, et al. Three-dimensional and four-dimensional transesophageal echocardiographic imaging of the heart and aorta in humans using a computed tomographic imaging probe. Echocardiography (Mount Kisco, NY) 1992;9:677-87.

43. Ota T, Kisslo J, von Ramm OT, Yoshikawa J. Real-time, volumetric echocardiography: usefulness of volumetric scanning for the assessment of cardiac volume and function. Journal of cardiology 2001;37 Suppl 1:93-101.

44. Sugeng L, Weinert L, Thiele K, Lang RM. Real-time three-dimensional echocardiography using a novel matrix array transducer. Echocardiography (Mount Kisco, NY) 2003;20:623-35.

45. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2004;17:630-3.

46. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2004;17:1021-9.

47. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. European heart journal cardiovascular Imaging 2012;13:1-46.

48. Todd AJ, Leslie SJ, Macdougall M, Denvir MA. Clinical features remain important for the diagnosis of infective endocarditis in the modern era. QJM : monthly journal of the Association of Physicians 2006;99:23-31.

49. Alagna L, Park LP, Nicholson BP, et al. Repeat endocarditis: analysis of risk factors based on the International Collaboration on Endocarditis - Prospective Cohort Study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2014;20:566-75.

50. Pelletier LL, Jr., Petersdorf RG. Infective endocarditis: a review of 125 cases from the University of Washington Hospitals, 1963-72. Medicine 1977;56:287-313.

51. Pedersen FK, Petersen EA. Bacterial endocarditis at Blegdamshospitalet in Copenhagen 1944-1973. Scandinavian journal of infectious diseases 1976;8:99-105.

52. Garvey GJ, Neu HC. Infective endocarditis--an evolving disease. A review of endocarditis at the Columbia-Presbyterian Medical Center, 1968-1973. Medicine 1978;57:105-27.

53. Lowes JA, Hamer J, Williams G, et al. 10 Years of infective endocarditis at St. Bartholomew's Hospital: analysis of clinical features and treatment in relation to prognosis and mortality. Lancet (London, England) 1980;1:133-6.

54. Welton DE, Young JB, Gentry WO, et al. Recurrent infective endocarditis: analysis of predisposing factors and clinical features. The American journal of medicine 1979;66:932-8.

55. Haddy RI, Westveer D, Gordon RC. Bacterial endocarditis in the community hospital. The Journal of family practice 1981;13:807-11.

56. Hammel T, Hirzel HO, Krayenbuhl HP. [Etiology and clinical course of bacterial endocarditis, 1971-1980]. Schweizerische medizinische Wochenschrift 1982;112:1592-6.

57. Venezio FR, Westenfelder GO, Cook FV, Emmerman J, Phair JP. Infective endocarditis in a community hospital. Archives of internal medicine 1982;142:789-92.

58. Bayliss R, Clarke C, Oakley CM, Somerville W, Whitfield AG, Young SE. The microbiology and pathogenesis of infective endocarditis. British heart journal 1983;50:513-9.

59. Terpenning MS, Buggy BP, Kauffman CA. Infective endocarditis: clinical features in young and elderly patients. The American journal of medicine 1987;83:626-34.

60. King JW, Nguyen VQ, Conrad SA. Results of a prospective statewide reporting system for infective endocarditis. The American journal of the medical sciences 1988;295:517-27.

61. Steckelberg JM, Melton LJ, 3rd, Ilstrup DM, Rouse MS, Wilson WR. Influence of referral bias on the apparent clinical spectrum of infective endocarditis. The American journal of medicine 1990;88:582-8.

62. Kim EL, Ching DL, Pien FD. Bacterial endocarditis at a small community hospital. The American journal of the medical sciences 1990;299:87-93.

63. Varstela E, Verkkala K, Pohjola-Sintonen S, Valtonen V, Maamies T. Surgical treatment of infective aortic valve endocarditis. Scandinavian journal of thoracic and cardiovascular surgery 1991;25:167-74.

64. Jaffe WM, Morgan DE, Pearlman AS, Otto CM. Infective endocarditis, 1983-1988: echocardiographic findings and factors influencing morbidity and mortality. Journal of the American College of Cardiology 1990;15:1227-33.

65. Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K. Epidemiologic aspects of infective endocarditis in an urban population. A 5-year prospective study. Medicine 1995;74:324-39.

66. Nissen H, Nielsen PF, Frederiksen M, Helleberg C, Nielsen JS. Native valve infective endocarditis in the general population: a 10-year survey of the clinical picture during the 1980s. European heart journal 1992;13:872-7.

67. Schon HR, Fuchs CJ, Schomig A, Blomer H. [Changes in infectious endocarditis--analysis of a disease picture in the last decade]. Zeitschrift fur Kardiologie 1994;83:31-7.

68. Gentry LO, Khoshdel A. New approaches to the diagnosis and treatment of infective endocarditis: review of 100 consecutive cases. Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 1989;16:250-7.

69. Watanakunakorn C, Burkert T. Infective endocarditis at a large community teaching hospital, 1980-1990. A review of 210 episodes. Medicine 1993;72:90-102.

70. Roberts WC, Oluwole BO, Fernicola DJ. Comparison of active infective endocarditis involving a previously stenotic versus a previously nonstenotic aortic valve. The American journal of cardiology 1993;71:1082-8.

71. Delahaye F, Goulet V, Lacassin F, et al. Characteristics of infective endocarditis in France in 1991. A 1-year survey. European heart journal 1995;16:394-401.

72. Selton-Suty C, Hoen B, Delahaye F, et al. Comparison of infective endocarditis in patients with and without previously recognized heart disease. The American journal of cardiology 1996;77:1134-7.

73. Tornos MP, Olona M, Permanyer-Miralda G, Almirante B, Evangelista A, Soler-Soler J. Is the clinical spectrum and prognosis of native valve infective endocarditis in non-addicts changing? European heart journal 1995;16:1686-91.

74. Rognon R, Kehtari R, Francioli P. Individual value of each of the Duke criteria for the diagnosis of infective endocarditis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 1999;5:396-403.

75. Sandre RM, Shafran SD. Infective endocarditis: review of 135 cases over 9 years. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1996;22:276-86.

76. Werner GS, Schulz R, Fuchs JB, et al. Infective endocarditis in the elderly in the era of transesophageal echocardiography: clinical features and prognosis compared with younger patients. The American journal of medicine 1996;100:90-7.

77. Ferreiros E, Nacinovich F, Casabe JH, et al. Epidemiologic, clinical, and microbiologic profile of infective endocarditis in Argentina: a national survey. The Endocarditis Infecciosa en la Republica Argentina-2 (EIRA-2) Study. American heart journal 2006;151:545-52.

78. Weng MC, Chang FY, Young TG, Ding YA. Analysis of 109 cases of infective endocarditis in a tertiary care hospital. Zhonghua yi xue za zhi = Chinese medical journal; Free China ed 1996;58:18-23.

79. Lamas CC, Eykyn SJ. Suggested modifications to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1997;25:713-9.

80. Bouza E, Menasalvas A, Munoz P, Vasallo FJ, del Mar Moreno M, Garcia Fernandez MA. Infective endocarditis--a prospective study at the end of the twentieth century: new predisposing conditions, new etiologic agents, and still a high mortality. Medicine 2001;80:298-307.

81. Castillo JC, Anguita MP, Ramirez A, et al. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. Heart (British Cardiac Society) 2000;83:525-30.

82. Mouly S, Ruimy R, Launay O, et al. The changing clinical aspects of infective endocarditis: descriptive review of 90 episodes in a French teaching hospital and risk factors for death. The Journal of infection 2002;45:246-56.

83. Abramczuk E, Hryniewiecki T, Stepinska J. Influence of pathogenetic factors on prognosis in patients with native valve infective endocarditis. Kardiologia polska 2006;64:675-81; discussion 82-3.

84. Cetinkaya Y, Akova M, Akalin HE, et al. A retrospective review of 228 episodes of infective endocarditis where rheumatic valvular disease is still common. International journal of antimicrobial agents 2001;18:1-7.

85. Fefer P, Raveh D, Rudensky B, Schlesinger Y, Yinnon AM. Changing epidemiology of infective endocarditis: a retrospective survey of 108 cases, 1990-1999. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2002;21:432-7.

86. Pachirat O, Chetchotisakd P, Klungboonkrong V, Taweesangsuksakul P, Tantisirin C, Loapiboon M. Infective endocarditis: prevalence, characteristics and mortality in Khon Kaen, 1990-1999. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 2002;85:1-10.

87. Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. Jama 2005;293:3022-8.

88. Netzer RO, Altwegg SC, Zollinger E, Tauber M, Carrel T, Seiler C. Infective endocarditis: determinants of long term outcome. Heart (British Cardiac Society) 2002;88:61-6.

89. Alestig K, Hogevik H, Olaison L. Infective endocarditis: a diagnostic and therapeutic challenge for the new millennium. Scandinavian journal of infectious diseases 2000;32:343-56.

90. Gotsman I, Meirovitz A, Meizlish N, Gotsman M, Lotan C, Gilon D. Clinical and echocardiographic predictors of morbidity and mortality in infective endocarditis: the significance of vegetation size. The Israel Medical Association journal : IMAJ 2007;9:365-9.

91. Koegelenberg CF, Doubell AF, Orth H, Reuter H. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. QJM : monthly journal of the Association of Physicians 2003;96:217-25.

92. Koegelenberg CF, Doubell AF, Orth H, Reuter H. Infective endocarditis: improving the diagnostic yield. Cardiovascular journal of South Africa : official journal for Southern Africa Cardiac Society [and] South African Society of Cardiac Practitioners 2004;15:14-20.

93. Castillo JC, Anguita MP, Torres F, et al. Comparison of features of active infective endocarditis involving native cardiac valves in nonintravenous drug users with and without predisposing cardiac disease. The American journal of cardiology 2002;90:1266-9.

94. Moura L, Zamorano J, Moreno R, et al. Perioperative mortality and long-term outcome of infective endocarditis. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de

Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2002;21:989-99.

95. Yoshinaga M, Niwa K, Niwa A, et al. Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. The American journal of cardiology 2008;101:114-8.

96. Chu J, Wilkins G, Williams M. Review of 65 cases of infective endocarditis in Dunedin Public Hospital. The New Zealand medical journal 2004;117:U1021.

97. Yousuf RM HS, Fauzi ARM., Shah A. Infective endocarditis in the East coast of peninsular Malaysia: a two year retrospective survey from Kuantan. JK-Practitioner 2006;13:5-8.

98. Cicalini S, Puro V, Angeletti C, Chinello P, Macri G, Petrosillo N. Profile of infective endocarditis in a referral hospital over the last 24 years. The Journal of infection 2006;52:140-6.

99. Nashmi A, Memish ZA. Infective endocarditis at a tertiary care centre in Saudi Arabia: review of 47 cases over 10 years. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 2007;13:64-71.

100. Hsu CN, Wang JY, Tseng CD, Hwang JJ, Hsueh PR, Liau CS. Clinical features and predictors for mortality in patients with infective endocarditis at a university hospital in Taiwan from 1995 to 2003. Epidemiology and infection 2006;134:589-97.

101. Jain V, Yang MH, Kovacicova-Lezcano G, Juhle LS, Bolger AF, Winston LG. Infective endocarditis in an urban medical center: association of individual drugs with valvular involvement. The Journal of infection 2008;57:132-8.

102. Hill EE, Herijgers P, Claus P, Vanderschueren S, Herregods MC, Peetermans WE. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. European heart journal 2007;28:196-203.

103. Giannitsioti E, Skiadas I, Antoniadou A, et al. Nosocomial vs. community-acquired infective endocarditis in Greece: changing epidemiological profile and mortality risk. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2007;13:763-9.

104. Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Annals of internal medicine 2009;150:586-94.

105. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Archives of internal medicine 2009;169:463-73.

106. Walls G, McBride S, Raymond N, et al. Infective endocarditis in New Zealand: data from the International Collaboration on Endocarditis Prospective Cohort Study. The New Zealand medical journal 2014;127:38-51.

107. Correa de Sa DD, Tleyjeh IM, Anavekar NS, et al. Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota. Mayo Clinic proceedings 2010;85:422-6.

108. Galvez-Acebal J, Rodriguez-Bano J, Martinez-Marcos FJ, et al. Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC infectious diseases 2010;10:17.

109. Pazdernik M, Baddour LM, Pelouch R. Infective endocarditis in the Czech Republic: eight years of experience at one of the country's largest medical centers. The Journal of heart valve disease 2009;18:395-400.

110. Tugcu A, Yildirimturk O, Baytaroglu C, et al. Clinical spectrum, presentation, and risk factors for mortality in infective endocarditis: a review of 68 cases at a tertiary care center in Turkey. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir 2009;37:9-18.

111. Mokhles MM, Ciampichetti I, Head SJ, Takkenberg JJ, Bogers AJ. Survival of surgically treated infective endocarditis: a comparison with the general Dutch population. The Annals of thoracic surgery 2011;91:1407-12.

112. Baskerville CA, Hanrahan BB, Burke AJ, Holwell AJ, Remond MG, Maguire GP. Infective endocarditis and rheumatic heart disease in the north of Australia. Heart, lung & circulation 2012;21:36-41.

113. Wong CW, Porter G, Tisch J, Young C. Outcome and prognostic factors on 57 cases of infective endocarditis in a single centre. The New Zealand medical journal 2009;122:54-62.

114. Khaled AA, Al-Noami AY, Al-Ansi M, Faiza AA. Clinical features and outcome of infective endocarditis in yemeni patients treated with empirical antibiotic therapy. Heart views : the official journal of the Gulf Heart Association 2010;11:2-9.

115. Mokhles MM, Ciampichetti I, van Domburg R, Cheng JM, Bogers AJ, Witsenburg M. Infective endocarditis in a tertiary referral hospital: long-term follow up. The Journal of heart valve disease 2012;21:118-24.

116. Nunes MC, Gelape CL, Ferrari TC. Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period: prognostic factors and in-hospital outcome. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2010;14:e394-8.

117. Erbay AR, Erbay A, Canga A, et al. Risk factors for in-hospital mortality in infective endocarditis: five years' experience at a tertiary care hospital in Turkey. The Journal of heart valve disease 2010;19:216-24.

118. Dzupova O, Machala L, Baloun R, Maly M, Benes J, Czech Infective Endocarditis Working G. Incidence, predisposing factors, and aetiology of infective endocarditis in the Czech Republic. Scandinavian journal of infectious diseases 2012;44:250-5.

119. Selton-Suty C, Celard M, Le Moing V, et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;54:1230-9.

120. Nomura A, Omata F, Furukawa K. Risk factors of mid-term mortality of patients with infective endocarditis. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2010;29:1355-60.

121. Fernandez-Hidalgo N, Almirante B, Tornos P, et al. Prognosis of left-sided infective endocarditis in patients transferred to a tertiary-care hospital--prospective analysis of referral bias and influence of inadequate antimicrobial treatment. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2011;17:769-75.

122. Leone S, Ravasio V, Durante-Mangoni E, et al. Epidemiology, characteristics, and outcome of infective endocarditis in Italy: the Italian Study on Endocarditis. Infection 2012;40:527-35.

123. Wu KS, Lee SS, Tsai HC, et al. Non-nosocomial healthcare-associated infective endocarditis in Taiwan: an underrecognized disease with poor outcome. BMC infectious diseases 2011;11:221.

124. Knudsen JB, Fuursted K, Petersen E, et al. Procalcitonin in 759 patients clinically suspected of infective endocarditis. The American journal of medicine 2010;123:1121-7.

125. Knudsen JB, Fuursted K, Petersen E, et al. Failure of clinical features of low probability endocarditis. The early echo remains essential. Scandinavian cardiovascular journal : SCJ 2011;45:133-8.

126. Ferraris L, Milazzo L, Ricaboni D, et al. Profile of infective endocarditis observed from 2003 - 2010 in a single center in Italy. BMC infectious diseases 2013;13:545.

127. Poesen K, Pottel H, Colaert J, De Niel C. Epidemiology of infective endocarditis in a large Belgian non-referral hospital. Acta clinica Belgica 2014;69:183-90.

128. Gupta A, Gupta A, Kaul U, Varma A. Infective endocarditis in an Indian setup: Are we entering the 'modern' era? Indian Journal of Critical Care Medicine 2013;17:140-7.

129. Mirabel M, Andre R, Barsoum Mikhail P, et al. Infective endocarditis in the Pacific: clinical characteristics, treatment and long-term outcomes. Open heart 2015;2:e000183.

130. Koeda C, Tashiro A, Itoh T, Okabayashi H, Nakamura M. Mild renal dysfunction on admission is an important prognostic predictor in patients with infective endocarditis: a retrospective single-center study. Internal medicine (Tokyo, Japan) 2013;52:1013-8.

131. Fernandez-Hidalgo N, Almirante B, Tornos P, et al. Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2012;18:E522-30.

132. Ferreira JP, Gomes F, Rodrigues P, et al. Left-sided infective endocarditis: analysis of in-hospital and medium-term outcome and predictors of mortality. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2013;32:777-84.

133. Rizzi M, Ravasio V, Carobbio A, et al. Predicting the occurrence of embolic events: an analysis of 1456 episodes of infective endocarditis from the Italian Study on Endocarditis (SEI). BMC infectious diseases 2014;14:230.

134. Korem M, Israel S, Gilon D, et al. Epidemiology of infective endocarditis in a tertiary-center in Jerusalem: a 3-year prospective survey. European journal of internal medicine 2014;25:550-5.

135. Turak O, Ozcan F, Isleyen A, et al. Usefulness of neutrophil-to-lymphocyte ratio to predict in-hospital outcomes in infective endocarditis. The Canadian journal of cardiology 2013;29:1672-8.

136. Chu VH, Park LP, Athan E, et al. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. Circulation 2015;131:131-40.

137. Olmos C, Vilacosta I, Sarria C, et al. Characterization and clinical outcome of patients with possible infective endocarditis. International journal of cardiology 2015;178:31-3.

138. Simsek-Yavuz S, Sensoy A, Kasikcioglu H, et al. Infective endocarditis in Turkey: aetiology, clinical features, and analysis of risk factors for mortality in 325 cases. International journal of

INFECTIOUS DISEASES : IJID : OFFICIAL PUBLICATION OF THE INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES 2015;30:106-14.

139. FUKUCHI T, IWATA K, OHJI G. FAILURE OF EARLY DIAGNOSIS OF INFECTIVE ENDOCARDITIS IN JAPAN--A RETROSPECTIVE DESCRIPTIVE ANALYSIS. MEDICINE 2014;93:E237.

140. GUPTA K, JAGADEESAN N, AGRAWAL N, BHAT P, NANJAPPA MC. CLINICAL, ECHOCARDIOGRAPHIC AND MICROBIOLOGICAL STUDY, AND ANALYSIS OF OUTCOMES OF INFECTIVE ENDOCARDITIS IN TROPICAL COUNTRIES: A PROSPECTIVE ANALYSIS FROM INDIA. THE JOURNAL OF HEART VALVE DISEASE 2014;23:624-32.

141. VERHEUGT CL, UITERWAAL CS, VAN DER VELDE ET, ET AL. TURNING 18 WITH CONGENITAL HEART DISEASE: PREDICTION OF INFECTIVE ENDOCARDITIS BASED ON A LARGE POPULATION. EUROPEAN HEART JOURNAL 2011;32:1926-34.

142. GERSONY WM, HAYES CJ, DRISCOLL DJ, ET AL. BACTERIAL ENDOCARDITIS IN PATIENTS WITH AORTIC STENOSIS, PULMONARY STENOSIS, OR VENTRICULAR SEPTAL DEFECT. CIRCULATION 1993;87:I121-6.

143. KEANE JF, DRISCOLL DJ, GERSONY WM, ET AL. SECOND NATURAL HISTORY STUDY OF CONGENITAL HEART DEFECTS. RESULTS OF TREATMENT OF PATIENTS WITH AORTIC VALVAR STENOSIS. CIRCULATION 1993;87:I16-27.

144. THELL R, MARTIN FH, EDWARDS JE. BACTERIAL ENDOCARDITIS IN SUBJECTS 60 YEARS OF AGE AND OLDER. CIRCULATION 1975;51:174-82.

145. ROBBINS N, DEMARIA A, MILLER MH. INFECTIVE ENDOCARDITIS IN THE ELDERLY. SOUTHERN MEDICAL JOURNAL 1980;73:1335-8.

146. GROSSMAN E, HOLTZMAN E, ROSENTHAL T, SHEMESH E, SAMRA Y, MICHAELI D. A COMPARATIVE STUDY OF INFECTIVE ENDOCARDITIS. ISRAEL JOURNAL OF MEDICAL SCIENCES 1984;20:389-93.

147. RUDOLPH W, KRAUS F. [DETECTION AND EVALUATION OF INFECTIOUS ENDOCARDITIS]. HERZ 1983;8:241-70.

148. HODES RM. ENDOCARDITIS IN ETHIOPIA. ANALYSIS OF 51 CASES FROM ADDIS ABABA. TROPICAL AND GEOGRAPHICAL MEDICINE 1993;45:70-2.

149. MANSUR AJ, GRINBERG M, BELLOTTI G, JATENE A, PILEGGI F. INFECTIVE ENDOCARDITIS IN THE 1980S: EXPERIENCE AT A HEART HOSPITAL. CLINICAL CARDIOLOGY 1990;13:623-30.

150. THAMLIKITKUL V, PRADITSUWAN R, PERMPIKUL C, JOOTAR P. NATIVE VALVE INFECTIVE ENDOCARDITIS AT SIRIRAJ HOSPITAL, 1982-1989. JOURNAL OF THE MEDICAL ASSOCIATION OF THAILAND = CHOTMAIHET THANGPHAET 1991;74:313-22.

151. Choudhury R, Grover A, Varma J, et al. Active infective endocarditis observed in an Indian hospital 1981-1991. The American journal of cardiology 1992;70:1453-8.

152. Benn M, Hagelskjaer LH, Tvede M. Infective endocarditis, 1984 through 1993: a clinical and microbiological survey. Journal of internal medicine 1997;242:15-22.

153. Netzer RO, Zollinger E, Seiler C, Cerny A. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980-1995. Heart (British Cardiac Society) 2000;84:25-30.

154. Dyson C, Barnes RA, Harrison GA. Infective endocarditis: an epidemiological review of 128 episodes. The Journal of infection 1999;38:87-93.

155. Cheng A, Athan E, Appelbe A, McDonald M. The changing profile of bacterial endocarditis as seen at an australian provincial centre. Heart, lung & circulation 2002;11:26-31.

156. Di Filippo S, Delahaye F, Semiond B, et al. Current patterns of infective endocarditis in congenital heart disease. Heart (British Cardiac Society) 2006;92:1490-5.

157. Tariq M, Siddiqui BK, Jadoon A, et al. Clinical profile and outcome of infective endocarditis at the Aga Khan University hospital. International Journal of Collaborative Research on Internal Medicine and Public Health 2009;1:84-99.

158. McKay G, Bunton R, Galvin I, Shaw D, Singh H. Infective endocarditis--a twelve year surgical outcome series. The New Zealand medical journal 2002;115:124-6.

159. Tariq M, Alam M, Munir G, Khan MA, Smego RA, Jr. Infective endocarditis: a five-year experience at a tertiary care hospital in Pakistan. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2004;8:163-70.

160. Cecchi E, Forno D, Imazio M, et al. New trends in the epidemiological and clinical features of infective endocarditis: results of a multicenter prospective study. Italian heart journal : official journal of the Italian Federation of Cardiology 2004;5:249-56.

161. Durante-Mangoni E, Bradley S, Selton-Suty C, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Archives of internal medicine 2008;168:2095-103.

162. Assiri AS. Clinical and microbiological profiles of infective endocarditis in a tertiary hospital in Aseer region, Saudi Arabia. Journal of the Saudi Heart Association 2011;23:207-11.

163. Nakatani S, Mitsutake K, Ohara T, Kokubo Y, Yamamoto H, Hanai S. Recent picture of infective endocarditis in Japan--lessons from Cardiac Disease Registration (CADRE-IE). Circulation journal : official journal of the Japanese Circulation Society 2013;77:1558-64.

164. Marks DJ, Hyams C, Koo CY, et al. Clinical features, microbiology and surgical outcomes of infective endocarditis: a 13-year study from a UK tertiary cardiothoracic referral centre. QJM : monthly journal of the Association of Physicians 2015;108:219-29.

165. Cecchi E, Chirillo F, Castiglione A, et al. Clinical epidemiology in Italian Registry of Infective Endocarditis (RIEI): Focus on age, intravascular devices and enterococci. International journal of cardiology 2015;190:151-6.

166. Ma XZ, Li XY, Que CL, Lv Y. Underlying heart disease and microbiological spectrum of adult infective endocarditis in one Chinese university hospital: a 10-year retrospective study. Internal medicine journal 2013;43:1303-9.

167. Begezsan, II, Dorobat CM. Diagnostic approaches in infective endocarditis. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 2012;116:108-13.

168. Collins JA, Zhang Y, Burke AP. Pathologic findings in native infective endocarditis. Pathology, research and practice 2014.

169. Conn HL, Horwitz O. Cardiac and vascular diseases. Philadelphia,: Lea & Febiger; 1971.

170. Rapaport E. Natural history of aortic and mitral valve disease. The American journal of cardiology 1975;35:221-7.

171. Chizner MA, Pearle DL, deLeon AC, Jr. The natural history of aortic stenosis in adults. American heart journal 1980;99:419-24.

172. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. European heart journal 1988;9 Suppl E:57-64.

173. Rahimtoola SH. Perspective on valvular heart disease: an update. Journal of the American College of Cardiology 1989;14:1-23.

174. McDicken WN, Sutherland GR, Moran CM, Gordon LN. Colour Doppler velocity imaging of the myocardium. Ultrasound in medicine & biology 1992;18:651-4.

175. Sutherland GR, Stewart MJ, Groundstroem KW, et al. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 1994;7:441-58.

176. Bonow RO, Carabello B, de Leon AC, et al. ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease. Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). The Journal of heart valve disease 1998;7:672-707.

177. Falase AO, Jaiyesimi F, Iyun AO, Attah EB. Infective endocarditis-experience in Nigeria. Tropical and geographical medicine 1976;28:9-15.

178. Bailey IK, Richards JG. Infective endocarditis in a Sydney teaching hospital--1962-1971. Australian and New Zealand journal of medicine 1975;5:413-20.

179. Singham KT, Anuar M, Puthucheary SD. Infective endocarditis 1968-1977: an Asian experience. Annals of the Academy of Medicine, Singapore 1980;9:435-9.

180. Arbulu A, Asfaw I. Management of infective endocarditis: seventeen years' experience. The Annals of thoracic surgery 1987;43:144-9.

181. Blackett K. Endocarditis in Cameroon. Journal of the Royal College of Physicians of London 1989;23:260-3.

182. Agarwal R, Bahl VK, Malaviya AN. Changing spectrum of clinical and laboratory profile of infective endocarditis. The Journal of the Association of Physicians of India 1992;40:721-3.

183. Iga K, Hori K, Matsumura T, Tomonaga G, Gen H, Tamamura T. Native valve infective endocarditis in adults--analysis of 32 consecutive cases over a ten-year period from 1980 to 1989. Japanese circulation journal 1991;55:437-42.

184. Manford M, Matharu J, Farrington K. Infective endocarditis in a district general hospital. Journal of the Royal Society of Medicine 1992;85:262-6.

185. Khanal B, Harish BN, Sethuraman KR, Srinivasan S. Infective endocarditis: report of a prospective study in an Indian hospital. Tropical doctor 2002;32:83-5.

186. Garg N, Kandpal B, Garg N, et al. Characteristics of infective endocarditis in a developing country-clinical profile and outcome in 192 Indian patients, 1992-2001. International journal of cardiology 2005;98:253-60.

187. Rehman S SG, Shahid M, Shahid M. Clinical presentation of infective endocarditis. J Postgrad Med Inst 2002;16:55-63.

188. Jain SR PJ, Phasalkar MA, Roy BH , Jayram AA , Shah SR , Singh T , Thakkar AS. Clinical Spectrum of Infective Endocarditis in a Tertiary Care Centre in Western India: A Prospective Study International Journal of Clinical Medicine 2014;5:177-87.

189. Danford HG, Danford DA, Mielke JE, Peterson LF. Echocardiographic evaluation of the hemodynamic effects of chronic aortic insufficiency with observations on left ventricular performance. Circulation 1973;48:253-62.

190. Bonow RO, Rosing DR, McIntosh CL, et al. The natural history of asymptomatic patients with aortic regurgitation and normal left ventricular function. Circulation 1983;68:509-17.

191. Jaffe WM, Roche AH, Coverdale HA, McAlister HF, Ormiston JA, Greene ER. Clinical evaluation versus Doppler echocardiography in the quantitative assessment of valvular heart disease. Circulation 1988;78:267-75.

192. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2003;16:777-802.

193. Mills P, Leech G, Davies M, Leathan A. The natural history of a non-stenotic bicuspid aortic valve. British heart journal 1978;40:951-7.

194. Fenoglio JJ, Jr., McAllister HA, Jr., DeCastro CM, Davia JE, Cheitlin MD. Congenital bicuspid aortic valve after age 20. The American journal of cardiology 1977;39:164-9.

195. Cassel GA, Haitas B, Lakier JB, Barlow JB. Infective endocarditis at the Johannesburg Hospital. A retrospective analysis of 40 patients. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 1979;55:624-7.

196. Auger P, Marquis G, Dyrda I, Martineau JP, Solymoss CB. Infective endocarditis update experience from a heart hospital. Acta cardiologica 1981;36:105-23.

197. Griffin MR, Wilson WR, Edwards WD, O'Fallon WM, Kurland LT. Infective endocarditis. Olmsted County, Minnesota, 1950 through 1981. Jama 1985;254:1199-202.

198. Woo KS, Lam YM, Kwok HT, Tse LK, Vallance-Owen J. Prognostic index in prediction of mortality from infective endocarditis. International journal of cardiology 1989;24:47-54.

199. Cheng JJ, Ko YL, Chang SC, et al. Retrospective analysis of 97 patients with infective endocarditis seen over the past 8 years. Taiwan yi xue hui za zhi Journal of the Formosan Medical Association 1989;88:213-7.

200. Borger MA, Preston M, Ivanov J, et al. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? The Journal of thoracic and cardiovascular surgery 2004;128:677-83.

201. Kiwan YA, Hayat N, Vijayaraghavan DG, et al. Infective endocarditis: a prospective study of 60 consecutive cases. Materia medica Polona Polish journal of medicine and pharmacy 1990;22:173-5.

202. Vlessis AA, Hovaguimian H, Jaggers J, Ahmad A, Starr A. Infective endocarditis: ten-year review of medical and surgical therapy. The Annals of thoracic surgery 1996;61:1217-22.

203. Jalal S, Khan KA, Alai MS, et al. Clinical spectrum of infective endocarditis: 15 years experience. Indian heart journal 1998;50:516-9.

204. Lamas CC, Eykyn SJ. Bicuspid aortic valve--A silent danger: analysis of 50 cases of infective endocarditis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2000;30:336-41.

205. Michelena HI, Desjardins VA, Avierinos JF, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation 2008;117:2776-84.

206. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. Jama 2011;306:1104-12.

207. Michelena HI, Prakash SK, Della Corte A, et al. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). Circulation 2014;129:2691-704.

208. Tran CT, Kjeldsen K. Endocarditis at a tertiary hospital: reduced acute mortality but poor long term prognosis. Scandinavian journal of infectious diseases 2006;38:664-70.

209. Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. Jama 2008;300:1317-25.

210. Heiro M, Helenius H, Makila S, et al. Infective endocarditis in a Finnish teaching hospital: a study on 326 episodes treated during 1980-2004. Heart (British Cardiac Society) 2006;92:1457-62.

211. Heiro M, Helenius H, Hurme S, et al. Long-term outcome of infective endocarditis: a study on patients surviving over one year after the initial episode treated in a Finnish teaching hospital during 25 years. BMC infectious diseases 2008;8:49.

212. Suzuki Y, Daitoku K, Minakawa M, Fukui K, Fukuda I. Infective endocarditis with congenital heart disease. The Japanese journal of thoracic and cardiovascular surgery : official publication of the Japanese Association for Thoracic Surgery = Nihon Kyobu Geka Gakkai zasshi 2006;54:297-300.

213. Collins MJ, Butany J, Borger MA, Strauss BH, David TE. Implications of a congenitally abnormal valve: a study of 1025 consecutively excised aortic valves. Journal of clinical pathology 2008;61:530-6.

214. Kahveci G, Bayrak F, Pala S, Mutlu B. Impact of bicuspid aortic valve on complications and death in infective endocarditis of native aortic valves. Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 2009;36:111-6.

215. Li L, Wang H, Wang L, Pu J, Zhao H. Changing profile of infective endocarditis: a clinicopathologic study of 220 patients in a single medical center from 1998 through 2009. Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 2014;41:491-8.

216. Tribouilloy C, Rusinaru D, Sorel C, et al. Clinical characteristics and outcome of infective endocarditis in adults with bicuspid aortic valves: a multicentre observational study. Heart (British Cardiac Society) 2010;96:1723-9.

217. Lu KJ, Kearney LG, Ord M, Jones E, Burrell LM, Srivastava PM. Age adjusted Charlson Co-morbidity Index is an independent predictor of mortality over long-term follow-up in infective endocarditis. International journal of cardiology 2013;168:5243-8.

218. Senthilkumar S, Menon T, Subramanian G. Epidemiology of infective endocarditis in Chennai, South India. Indian journal of medical sciences 2010;64:187-91.

219. Sadaka M, ElSharkawy E, Soliman M, El-Din AN, El-Hay MAA. Study of infective endocarditis in Alexandria main university hospitals. Egyptian Heart Journal 2013;65:307-17.

220. Baek JE, Park SJ, Woo SB, Choi JY, Jung JW, Kim NK. Changes in patient characteristics of infective endocarditis with congenital heart disease: 25 years experience in a single institution. Korean circulation journal 2014;44:37-41.

221. Elbey MA, Akdag S, Kalkan ME, et al. A multicenter study on experience of 13 tertiary hospitals in Turkey in patients with infective endocarditis. Anadolu kardiyoloji dergisi : AKD = the Anatolian journal of cardiology 2013;13:523-7.

222. Nanda NC, Gramiak R, Manning J, Mahoney EB, Lipchik EO, DeWeese JA. Echocardiographic recognition of the congenital bicuspid aortic valve. Circulation 1974;49:870-5.

223. Devereux RB, Hawkins I, Kramer-Fox R, et al. Complications of mitral valve prolapse. Disproportionate occurrence in men and older patients. The American journal of medicine 1986;81:751-8.

224. MacMahon SW, Hickey AJ, Wilcken DE, Wittes JT, Feneley MP, Hickie JB. Risk of infective endocarditis in mitral valve prolapse with and without precordial systolic murmurs. The American journal of cardiology 1987;59:105-8.

225. Danchin N, Voiriot P, Briancon S, et al. Mitral valve prolapse as a risk factor for infective endocarditis. Lancet (London, England) 1989;1:743-5.

226. Zuppiroli A, Mori F, Favilli S, et al. "Natural histories" of mitral valve prolapse. Influence of patient selection on cardiovascular event rates. Italian heart journal : official journal of the Italian Federation of Cardiology 2001;2:107-14.

227. Mills P, Rose J, Hollingsworth J, Amara I, Craige E. Long-term prognosis of mitral-valve prolapse. The New England journal of medicine 1977;297:13-8.

228. Corrigall D, Bolen J, Hancock EW, Popp RL. Mitral valve prolapse and infective endocarditis. The American journal of medicine 1977;63:215-22.

229. Nishimura RA, McGoon MD, Shub C, Miller FA, Jr., Ilstrup DM, Tajik AJ. Echocardiographically documented mitral-valve prolapse. Long-term follow-up of 237 patients. The New England journal of medicine 1985;313:1305-9.

230. Tresch DD, Sigel R, Keelan MH, Jr., Gross CM, Brooks HL. Mitral valve prolapse in the elderly. Journal of the American Geriatrics Society 1979;27:421-4.

231. Roucaut G, Beaune J, Malquarti V, Rabatel J, Froment A. Mitral valve prolapse and infective endocarditis. European heart journal 1984;5 Suppl C:81-5.

232. Duren DR, Becker AE, Dunning AJ. Long-term follow-up of idiopathic mitral valve prolapse in 300 patients: a prospective study. Journal of the American College of Cardiology 1988;11:42-7.

233. Skehan JD, Murray M, Mills PG. Infective endocarditis: incidence and mortality in the North East Thames Region. British heart journal 1988;59:62-8.

234. Vered Z, Oren S, Rabinowitz B, Meltzer RS, Neufeld HN. Mitral valve prolapse. Quantitative analysis and long-term follow-up. Israel journal of medical sciences 1985;21:644-8.

235. Naggar CZ, Pearson WN, Seljan MP. Frequency of complications of mitral valve prolapse in subjects aged 60 years and older. The American journal of cardiology 1986;58:1209-12.

236. Peat EB, Lang SD. Infective endocarditis in a racially mixed community: a 10 year review of 78 cases. The New Zealand medical journal 1989;102:33-6.

237. Wells AU, Fowler CC, Ellis-Pegler RB, Luke R, Hannan S, Sharpe DN. Endocarditis in the 80s in a general hospital in Auckland, New Zealand. The Quarterly journal of medicine 1990;76:753-62.

238. Marks AR, Choong CY, Sanfilippo AJ, Ferre M, Weyman AE. Identification of high-risk and low-risk subgroups of patients with mitral-valve prolapse. The New England journal of medicine 1989;320:1031-6.

239. Kim S, Kuroda T, Nishinaga M, et al. Relationship between severity of mitral regurgitation and prognosis of mitral valve prolapse: echocardiographic follow-up study. American heart journal 1996;132:348-55.

240. Siddiq S, Missri J, Silverman DI. Endocarditis in an urban hospital in the 1990s. Archives of internal medicine 1996;156:2454-8.

241. Yeo TC, Lim MC, Cheng KL, See Tho ML, Ng WL, Choo MH. Clinical and echocardiographic features of mitral valve prolapse patients in a local population. Singapore medical journal 1996;37:143-6.

242. Borer A, Riesenberg K, Uriel N, et al. Infective endocarditis in a tertiary-care hospital in southern Israel. Public health reviews 1998;26:317-30.

243. Ako J, Ikari Y, Hatori M, Hara K, Ouchi Y. Changing spectrum of infective endocarditis: review of 194 episodes over 20 years. Circulation journal : official journal of the Japanese Circulation Society 2003;67:3-7.

244. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. Jama 2002;288:75-81.

245. Loupa C, Mavroidi N, Boutsikakis I, et al. Infective endocarditis in Greece: a changing profile. Epidemiological, microbiological and therapeutic data. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2004;10:556-61.

246. Yiu KH, Siu CW, Lee KL, et al. Emerging trends of community acquired infective endocarditis. International journal of cardiology 2007;121:119-22.

247. Knudsen JB, Fuursted K, Petersen E, et al. Infective endocarditis: a continuous challenge. The recent experience of a European tertiary center. The Journal of heart valve disease 2009;18:386-94.

248. Math RS, Sharma G, Kothari SS, et al. Prospective study of infective endocarditis from a developing country. American heart journal 2011;162:633-8.

249. Scudeller L, Badano L, Crapis M, Pagotto A, Viale P. Population-based surveillance of infectious endocarditis in an Italian region. Archives of internal medicine 2009;169:1720-3.

250. Castillo JC, Anguita MP, Ruiz M, et al. Changing epidemiology of native valve infective endocarditis. Revista espanola de cardiologia (English ed) 2011;64:594-8.

251. Nakagawa T, Wada H, Sakakura K, et al. Clinical features of infective endocarditis: comparison between the 1990s and 2000s. Journal of cardiology 2014;63:145-8.

252. Sun BJ, Choi SW, Park KH, et al. Infective endocarditis involving apparently structurally normal valves in patients without previously recognized predisposing heart disease. Journal of the American College of Cardiology 2015;65:307-9.

253. Hajihossainlou B, Heidarnia MA, Sharif Kashani B. Changing pattern of infective endocarditis in Iran: A 16 years survey. Pakistan journal of medical sciences 2013;29:85-90.

254. Al Abri SS, Zahedi FI, Kurup PJ, Al-Jardani AK, Beeching NJ. The epidemiology and outcomes of infective endocarditis in a tertiary care hospital in Oman. Journal of infection and public health 2014;7:400-6.

255. Watt G, Pachirat O, Baggett HC, et al. Infective endocarditis in northeastern Thailand. Emerging infectious diseases 2014;20:473-6.

256. Barlow JB, Bosman CK. Aneurysmal protrusion of the posterior leaflet of the mitral valve. An auscultatory-electrocardiographic syndrome. American heart journal 1966;71:166-78.

257. Barlow JB, Bosman CK, Pocock WA, Marchand P. Late systolic murmurs and non-ejection ("mid-late") systolic clicks. An analysis of 90 patients. British heart journal 1968;30:203-18.

258. Engle MA. The syndrome of apical systolic click, late systolic murmur, and abnormal T waves. Circulation 1969;39:1-2.

259. Popp RL, Brown OR, Silverman JF, Harrison DC. Echocardiographic abnormalities in the mitral valve prolapse syndrome. Circulation 1974;49:428-33.

260. Weiss AN, Mimbs JW, Ludbrook PA, Sobel BE. Echocardiographic detection of mitral valve prolapse. Exclusion of false positive diagnosis and determination of inheritance. Circulation 1975;52:1091-6.

261. Devereux RB, Perloff JK, Reichek N, Josephson ME. Mitral valve prolapse. Circulation 1976;54:3-14.

262. Barron JT, Manrose DL, Liebson PR, Cheng TO. Comparison of auscultation with two-dimensional and Doppler echocardiography in patients with suspected mitral valve prolapse. Clinical cardiology 1988;11:A30.

263. Levine RA, Triulzi MO, Harrigan P, Weyman AE. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation 1987;75:756-67.

264. Shah PM. Current concepts in mitral valve prolapse--diagnosis and management. Journal of cardiology 2010;56:125-33.

265. Kennedy JW, Yarnall SR, Murray JA, Figley MM. Quantitative angiocardiography. IV. Relationships of left atrial and ventricular pressure and volume in mitral valve disease. Circulation 1970;41:817-24.

266. Rahimtoola SH, Frye RL. Valvular heart disease. Circulation 2000;102:IV24-33.

267. Colman AL, Keefe JF, Wolk MJ, Levine HJ. Isolated tricuspid valvular stenosis. The American journal of cardiology 1970;26:443-4.

268. Keefe JF, Wolk MJ, Levine HJ. Isolated tricuspid valvular stenosis. The American journal of cardiology 1970;25:252-7.

269. Morgan JR, Forker AD. Isolated tricuspid insufficiency. Circulation 1971;43:559-64.

270. Morgan JR, Forker AD, Coates JR, Myers WS. Isolated tricuspid stenosis. Circulation 1971;44:729-32.

271. Waggoner AD, Quinones MA, Young JB, et al. Pulsed Doppler echocardiographic detection of right-sided valve regurgitation. Experimental results and clinical significance. The American journal of cardiology 1981;47:279-86.

272. Thiene G, Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology 2006;15:256-63.

273. Dodo H, Perloff JK, Child JS, Miner PD, Pegues DA. Are high-velocity tricuspid and pulmonary regurgitation endocarditis risk substrates? American heart journal 1998;136:109-14.

274. Hayes CJ, Gersony WM, Driscoll DJ, et al. Second natural history study of congenital heart defects. Results of treatment of patients with pulmonary valvar stenosis. Circulation 1993;87:I28-37.

275. Sawae Y. Current diagnosis of infective endocarditis. Japanese circulation journal 1985;49:519-28.

276. Verheul HA, van den Brink RB, van Vreeland T, Moulijn AC, Duren DR, Dunning AJ. Effects of changes in management of active infective endocarditis on outcome in a 25-year period. The American journal of cardiology 1993;72:682-7.

277. JOHNSON LW, GROSSMAN W, DALEN JE, DEXTER L. PULMONIC STENOSIS IN THE ADULT. LONG-TERM FOLLOW-UP RESULTS. THE NEW ENGLAND JOURNAL OF MEDICINE 1972;287:1159-63.

278. BRUCE CJ, CONNOLLY HM. RIGHT-SIDED VALVE DISEASE DESERVES A LITTLE MORE RESPECT. CIRCULATION 2009;119:2726-34.

279. HABIB G, DERUMEAUX G, AVIERINOS JF, ET AL. VALUE AND LIMITATIONS OF THE DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY 1999;33:2023-9.

280. HICKIE JB. BACTERIAL ENDOCARDITIS, IN SYDNEY 1950-1959. THE MEDICAL JOURNAL OF AUSTRALIA 1961;1:929-34.

281. HORSTKOTTE D, FOLLATH F, GUTSCHIK E, ET AL. GUIDELINES ON PREVENTION, DIAGNOSIS AND TREATMENT OF INFECTIVE ENDOCARDITIS EXECUTIVE SUMMARY; THE TASK FORCE ON INFECTIVE ENDOCARDITIS OF THE EUROPEAN SOCIETY OF CARDIOLOGY. EUROPEAN HEART JOURNAL 2004;25:267-76.

282. STEWART JA, SILIMPERI D, HARRIS P, WISE NK, FRAKER TD, JR., KISSLO JA. ECHOCARDIOGRAPHIC DOCUMENTATION OF VEGETATIVE LESIONS IN INFECTIVE ENDOCARDITIS: CLINICAL IMPLICATIONS. CIRCULATION 1980;61:374-80.

283. KLUG D, LACROIX D, SAVOYE C, ET AL. SYSTEMIC INFECTION RELATED TO ENDOCARDITIS ON PACEMAKER LEADS: CLINICAL PRESENTATION AND MANAGEMENT. CIRCULATION 1997;95:2098-107.

284. HICKEY AJ, MACMAHON SW, WILCKEN DE. MITRAL VALVE PROLAPSE AND BACTERIAL ENDOCARDITIS: WHEN IS ANTIBIOTIC PROPHYLAXIS NECESSARY? AMERICAN HEART JOURNAL 1985;109:431-5.

285. SERVY A, VALEYRIE-ALLANORE L, ALLA F, ET AL. PROGNOSTIC VALUE OF SKIN MANIFESTATIONS OF INFECTIVE ENDOCARDITIS. JAMA DERMATOLOGY 2014;150:494-500.

286. VAN DER VELDE ET, VRIEND JW, MANNENS MM, UITERWAAL CS, BRAND R, MULDER BJ. CONCOR, AN INITIATIVE TOWARDS A NATIONAL REGISTRY AND DNA-BANK OF PATIENTS WITH CONGENITAL HEART DISEASE IN THE NETHERLANDS: RATIONALE, DESIGN, AND FIRST RESULTS. EUROPEAN JOURNAL OF EPIDEMIOLOGY 2005;20:549-57.

287. FEIGENBAUM H. ECHOCARDIOGRAPHY IN THE MANAGEMENT OF MITRAL VALVE PROLAPSE. AUSTRALIAN AND NEW ZEALAND JOURNAL OF MEDICINE 1992;22:550-5.

288. ZUPPIROLI A, RINALDI M, KRAMER-FOX R, FAVILLI S, ROMAN MJ, DEVEREUX RB. NATURAL HISTORY OF MITRAL VALVE PROLAPSE. THE AMERICAN JOURNAL OF CARDIOLOGY 1995;75:1028-32.

13 Table with Additional Information for All Studies

Reference	Inclusion Criteria	# of Patients	Initial Population	Study Design
Abramczuk[83]	NVIE (Duke criteria[3])	152	Mean age 46 y (range 10–76 y) 76% male 0% PVIE	Retrospective, single centre
Agarwal[182]	IE (von Reyn criteria[4])	28	Mean age 24 y ± 11 y 75% male 25% CHD	Single centre, probably prospective, but not clearly stated
Ako[243]	IE (Duke criteria[3])	194	Age range 6–82 y 71% male 0% IVDU 6% CHD 22% PVIE	Single centre, retrospective (admission records)
Al Abri[254]	Discharge code of IE (ICD 10-133.0), and analysis according to modified Duke criteria[1]	58	Mean age 44 y (range 14–85 y) 69% male 16% PVIE 9% CHD 5% IVDU	Single centre, retrospective (computerised activity register)
Alagna[49]	Possible or definite IE (Duke criteria[3])	1874	68% male 24% PVIE 9% IVDU 9% CHD	Prospective, multicentre
Alestig[89]	Diagnosis of IE, not specified. Most likely also includes autopsies	98	Not specified	Prospective clinical studies carried out in Göteborg since 1984, data obtained from a Swedish national registry of IE since 1995 and existing literature
Arbulu[180]	Patient with IE (criteria not mentioned)	417	62% male 67% IVDU 3% CHD	Retrospective, single centre
Assiri[162]	Definite IE (modified Duke criteria[1])	44	Mean age 31 ± 16 y (range 13–65 y)	Retrospective, single centre

			64% male 23% PVIE	
Auger[196]	IE (Pelletier[50] criteria)	50	Mean age 43 y 48% PVIE	Retrospective, single centre
Baek[220]	Definite IE (modified Duke criteria[1])	325	28% CHD	Retrospective, single centre
Bailey[178]	IE (Hickie definition[280])	202	Mean age 43 y 63% male 18% CHD 8% PVIE	Retrospective, single centre
Baskerville[112]	IE (modified Duke criteria[1]) Inclusion of most recent case in patient with multiple episodes	89	Median age 45 y (IQR 36–61) 63% male 19% PVIE 9% CHD 17% IVDU	Retrospective review (medical records), multicentre
Bayliss[58]	IE (criteria not specified)	541	Mean age 52 y (range 2–87 y) 67% male 4% CHD 1% IVDU 14% PVIE	Retrospective, multicentre (British Isles)
Begezsan[167]	IE (Duke criteria[3])	45	Mean age 49 y (range 9–76 y) 78% male	Retrospective, single centre
Benito[104]	Definite NVIE (modified Duke criteria[1]), in non-IVDU and an identified place of acquisition	253	62% male 0% IVDU	Prospective cohort study, multicentre (data from the ICE-PCS)
Benn[152]	IE or suspected IE (von Reyn criteria[4])	59	Mean age 55 y (range 15–83 y) 71% male 12% CHD 15% PVIE 5% IVDU	Retrospective, multicentre
Beton[21]	Echocardiographically diagnosed MVP	182	Mean age 48 y (range 12–87 y) 55% male	Prospective, single centre

Blackett[181]	IE in patients >8 y, criteria: Clinical features suggestive of IE (fever, deteriorating general health, weight loss, sweating, anaemia, clubbing, splenomegaly) with echocardiography showing thickening of valve, changing valve morphology or vegetations and had blood cultures done on at least 3 occasions. Positive blood cultures or all other clinical and paraclinical features of IE despite negative blood cultures	20	Mean age 26.8 y (range 8–70 y) 55% male 10% PVIE	Prospective, single centre
Borer[242]	Definite or possible IE (Duke criteria[3]) >15 y	71	Mean age 55 y (range 16–84 y) 55% male 1% IVDU 29% PVIE 11% CHD	Retrospective, single centre
Borger[200]	Aortic valve replacement patients with BAV		Mean age 56 y ± 15 y 76% male	Retrospective, single centre
Bouza[80]	IE, criteria (1 or more): (1) Clinical IE (von Reyn[4], Steckelberg,[61] or Duke criteria[3]) (2) Echocardiographic evidence of IE (3) Bloodstream infections by *S. viridans*, *S. bovis*, HACEK, *S. aureus*, *Enterococcus* spp. were screened (4) Histologic findings of IE	109	Mean age 50 y (range 19–89 y) 73% male 16.5% PVIE 36% IVDU	Prospective observational case series, single centre
Cassel[195]	IE (criteria not clearly specified) in adults	40	Mean age 43 y (range 13–69 y) 43% male 15% CHD 13% PVIE	Retrospective, single centre

Castillo[81]	IE (von Reyn criteria[4] until 1994 and Duke criteria[3] thereafter) in non-IVDU	138	Mean age 40 y ± 20 y (range 0–72 y) 0% IVDU 21% CHD 31% PVIE	Prospective case series, single centre
Castillo[250]	NVIE (von Reyn criteria[4] until 1994, Duke criteria[3] until 2000, modified Duke criteria[1] until 2004, and from 2004 definition according to ESC[281]) in non-IVDU	228	Mean age 50 ± 20 y 66% male 0% IVDU 0% PVIE	Prospective, single centre
Castillo[93]	Definite NVIE (von Reyn criteria[4] until 1994, Duke criteria[3] thereafter [and retrospectively applied to all cases]) in non-IVDU	154	60% male 0% PVIE 32% CHD	Prospective observational, multicentre
Cecchi[165]	Patient with definite IE (modified Duke criteria[1])	677	Median age 62 y (range 13–91 y) 73% male 12% IVDU 26% PVIE 6% CHD	Prospective, multicentre
Cecchi[160]	Definite IE (Duke criteria)[3] after confirmation by autopsy, pathology, or surgery data or 3-month follow-up data	147	10% IVDU 25% PVIE	Prospective, multicentre
Cetinkaya[84]	Diagnostic codes for IE from patient records in ID sections and autopsy records (Duke criteria[3] and von Reyn criteria[4] and additional minor criteria to Duke by Lamas[79])	147	Mean age 34 y ± 14 y (range 16–75 y) 57% male 20% PVIE 5% CHD 0% IVDU	Retrospective (hospital charts) review, single centre
Cheng[155]	IE (Duke criteria)[3]	58	Median age 63 y (range 20–94 y) 71% male	Retrospective, multicentre

			0% IVDU 31% PVIE	
Cheng[199]	IE, criteria: Definite: Direct evidence of IE noted at surgery Probable: Positive blood cultures plus at least 3 of the following: fever, predisposing heart disease or new regurgitant murmur, systemic embolism, and echocardiographic evidence of valvular vegetation Possible: (A) Positive blood cultures with fever, and predisposing heart condition or new regurgitant murmur (B) Negative blood cultures with all 3 of the following: fever, predisposing heart disease, echocardiographic evidence of valvular vegetation or systemic embolisation	97	Mean age 39 y ± 16 y (range 14-76 y) 60% male 21% CHD 20% PVIE	Retrospective, single centre
Choudhury[151]	IE, criteria: (1) Demonstration of a vegetation on 2D echocardiography in accordance with Stewart et al.[282] (2) ≥2 positive blood cultures growing the same organism(s) with the presence of ≥2 of the following – fever lasting for >3 days, evidence of systemic or septic pulmonary emboli in the presence of heart disease, changing murmur or appearance of a new murmur during hospitalisation, recent worsening of heart failure, and presence of certain features strongly associated with IE such as fundal	186	Mean age 25 y ± 12 y (range 2–75 y) 72% male 33% CHD 1% PVIE 1% IVDU	Retrospective, single centre

	haemorrhages, mycotic aneurysms, Osler's nodes			
Chu[96]	Definite and possible IE (Duke criteria (1994)[3])	65	Mean age 65 y ± 18 y (range 7–89 y) 68% male 24% PVIE 13% CHD	Retrospective, single centre
Chu[136]	Definite left-sided, non-cardiac device-related IE (modified Duke criteria[1])	1296	Median age 62 y (IQR 47–72) 68% male 25% PVIE 5% IVDU	Prospective cohort study, multicentre (ICE-PLUS cohort)
Cicalini[98]	Definite IE (Duke criteria[3])	283	Mean age 39 y ± 15 y 67% male 12% PVIE 60% IVDU	Retrospective (patient records), single centre
Clemens[20]	IE in patients with no predisposing heart conditions except for MVP, criteria: Either pathological documentation of bacterial endocarditis or fulfilment of clinical criteria Clinical criteria: Heart murmur, at least 2 blood cultures obtained at separate times and yielding the same organism, and at least 1 of the following: new or changed heart murmur, peripheral stigmata of IE on physical examination, or laboratory evidence of endocarditis	51	Mean age 47 y ± 18 y 63% male 27% IVDU 0% PVIE 0% CHD	
Collins[168]	Patients undergoing valve replacement surgery due to IE (criteria not defined)	95	Mean age 51 y 67% male 0% PVIE 25% IVDU	Prospective observational, single centre
Collins[213]	Patients with aortic valve replacement	1025		Retrospective, single centre

Correa de Sa[107]	Possible or definitive IE (modified Duke criteria[1]) in patients ≥18 y	150	67% male 7% CHD 22% PVIE	Retrospective, multicentre
Corrigall[228]	IE (criteria not clearly stated)	25	Mean age 47 y (range 19–69 y) 62% male	Retrospective, single centre
Danchin[225]	Mitral valve NVIE, criteria: Pathological evidence of IE at operation or necropsy, or fever and 2 major criteria, or fever, 1 major and 3 minor criteria Major criteria: at least 2 positive blood cultures, new or changing heart murmur, and typical echocardiographic vegetation Minor criteria: arterial embolism, immunological disorders, splenomegaly, regurgitation murmur, congestive heart failure, pre-existing heart disease, clinical signs of vasculitis	48	70% male 0% PVIE	Retrospective case-control study, single centre
Delahaye[71]	IE (modified from von Reyn)[4]: Definite: Direct evidence of IE based on macroscopy and/or histology from surgery or autopsy, and/or bacteriology (Gram stain or culture) of valvular vegetation or peripheral embolus Probable: (A) Persistently positive blood cultures plus 1 of the following: (1) New regurgitant murmur, or (2) Predisposing heart disease and vascular phenomena (at least 2), or (3) Predisposing heart disease and echocardiographic vegetation, or (4) Vascular phenomena (at least 2) and echocardiographic	415	Mean age 56 y ± 19 y (range 0–91 y) 64% male 22% PVIE 5% IVDU	Prospective survey, multicentre

	vegetation (B) Negative or intermittently positive blood cultures plus 1 of the following: (1) Fever and new regurgitant murmur and vascular phenomenal (at least 2), or (2) Fever and predisposing heart disease and vascular phenomena (at least 2) and echocardiographic vegetation Possible: (A) Persistently positive blood cultures plus 1 of the following: (1) Predisposing heart disease, or (2) Vascular phenomena (at least 2) (B) Negative or intermittently positive blood cultures plus all 3 of the following: (1) Fever (2) Predisposing heart disease, and (3) Vascular phenomenal (at least 2) Persistently positive blood cultures: At least 2 blood cultures obtained, with 2 of 2 positive, 3 of 3 positive, or at least 70% of cultures positive if 4 or more cultures obtained Vascular phenomena: Petechiae, splinter haemorrhages, conjunctival haemorrhages, Roth spots, Osier's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, and pulmonary, central nervous system, coronary, or peripheral emboli Intermittently positive blood culture: Any rate of blood culture positivity that does not need the definition of persistently positive	

Devereux[223]	NVIE patients (diagnostic criteria not further specified) with M-Mode and 2D echocardiography studies and isolated, pure, moderate to severe mitral regurgitation by clinical criteria (not further specified)	141	68% male 0% PVIE	Case-control study, single centre
Di Filippo[156]	Definite IE (Duke criteria[3]) in children and adults with CHD	153	Mean age 13 y ± 11% 57% male 5% PVIE 100% CHD	Retrospective, single centre
Dodo[273]	Adult patients with CHD who had pulmonary vascular disease with inherently normal pulmonary and tricuspid valves	186	Mean age 39 y ± 9 y (range 22–68 y) 42% male 100% CHD 0% PVIE	Prospective, observational, single centre
Durante-Mangoni[161]	Definite IE (modified Duke criteria[1])	2759	20% PVIE 10% IVDU	Prospective, multicentre (ICE cohort)
Duren[232]	Idiopathic mitral valve prolapse	300	Mean age 42 y (range 10–87 y) 45% male	Prospective, single centre
Dyson[154]	Microbiologically positive NVIE, criteria: (1) There were at least 2 positive blood cultures (yielding identical isolates) or a positive valve culture or positive serology. (2) There was evidence (echocardiographic or histopathological) of endocardial involvement and/or evidence of any 3 of the following: (i) predisposing heart condition, (ii) fever (>38.0°C), (iii) vascular phenomena (e.g. arterial emboli, intracranial haemorrhages, conjunctival haemorrhages), (iv) immunological	77	Mean age 53 y 70% male 0% PVIE 27% CHD 0% IVDU	Retrospective, single centre

	phenomena (e.g. glomerulonephritis, Osler's nodes, Roth spots)			
Dzupova[118]	Possible or definite IE (modified Duke criteria[1]) in patients with permanent residence in defined catchment area of each participating hospital during specified time	122	Median age 63 y (range 18–98 y) 66% male 7.5% IVDU 38% PVIE 11% CHD	Prospective, multicentre
Elbey[221]	Definite NVIE (modified Duke criteria[1])	158	Mean age 47 y ± 18 y (range 13–87 y) 55% male 0% PVIE 7% CHD	Retrospective, multicentre
Erbay[117]	Definite IE (modified Duke criteria[1]), exclusion of pacemaker patients	107	Mean age 45 y ± 16 y (range 19–77 y) 73% male 0% IVDU 44% PVIE 7% CHD	Retrospective, single centre
Falase[177]	IE, criteria (2 or more): (1) Repeatedly positive blood cultures during a febrile illness in a patient with previous valvular or congenital heart disease (2) Evidence of peripheral manifestation IE (3) Prolonged febrile illness and development of a significant murmur while under observation (4) Favourable response to antibiotic therapy	90	56% male	Retrospective, single centre
Fefer[85]	IE (von Reyn[4] or Duke criteria[3])	108	Mean age 57 y ± 22 y 56% male	Retrospective (medical records), single centre

			31% PVI 19% CHD	
Fenoglio[194]	Congenital BAV in patients ≥20 y in pathology samples (valves or hearts or photographs or autopsy descriptions)	152	100% CHD 0% PVIE	Retrospective, single centre
Fernandez-Hidalgo[131]	Definite or possible LSIE (modified Duke criteria[1]) in adult patients (≥18 y)	438	Mean age 66 y (IQR 51.8–74.9) 65% male 23% PVIE 3% IVDU	Prospective observational cohort study, single centre
Fernandez-Hidalgo[121]	Definite or possible LSIE (modified Duke criteria[1]) in adult patients (≥18 y)	334	66% male 21% PVIE 8% CHD	Prospective observational cohort study, single centre
Ferraris[126]	Possible or definite NVIE (modified Duke criteria[1])	111	Median age 53 y (IQR 42–71) 65% male 0% PVIE 30% IVDU 5% CHD	Retrospective, single centre
Ferreira[132]	Possible or definite LSIE (modified Duke criteria[1])	147	Median age 63 y (IQR 45–74) 71% male 13% PVIE 8% CHD	Retrospective, multicentre (2 hospitals)
Ferreiros[77] **EIRA-2 data (1992-1993)**	IE (Duke criteria[3]) in adult patients (>18 y)	294	Mean age 52 y ± 19 y 70% male 14% IVDU 9% PVIE	Prospective registry, multicentre
Ferreiros[77] **new data (2001-2002)**	IE (modified Duke criteria[1]) in adult patients (>18 y)	470	Mean age 58 y ± 18 y 70% male 4% IVDU 19% PVIE	Prospective, multicentre
Fukuchi[139]	Definite IE (modified Duke criteria[1])	82	Mean age 61 y ± 15 y 65% male 4% CHD 0% IVDU	Prospective, multicentre

			12% PVIE	
Galvez-Acebal[108]	LSIE (Duke criteria[3])	705	Median age 56 y (IQR 41–68 y) 69% male 24% PVIE 7% IVDU	Observational multicentre study
Garg[186]	Definite IE (Duke criteria[3])	192	Mean age 28 y ± 13 y (range 4–68 y) 73% male 29% CHD 10% PVIE 2% IVDU	Retrospective, single centre
Garvey[52]	IE, criteria: At least 2 positive blood cultures prior to initiation of therapy, surgical confirmation by pathologic abnormality and/or culture of the heart valve at operation or autopsy confirmation, or single positive culture and compatible course of disease, or clinical presentation only with convincing response and clinical presentation	154	60% male 7% IVDU 6% CHD 21% PVIE	Retrospective analysis of patient records, autopsy files, and files of the infectious diseases department
Gentry[68]	IE (criteria not stated)	94	Mean age 53 y (range 20–86 y) 80% male 13% CHD 43% PVIE 4% IVDU	Retrospective review, single centre
Gersony[142]	Patients included in the First Natural History Study of Congenital Heart Defects (NHS-1), meaning patients with AS or PS	2401	100% CHD	Prospective cohort study, multicentre
Giannitsioti[103]	Definite or possible IE (modified Duke criteria[1])	195	65% male 7% IVDU 22% PVIE	Prospective cohort study, multicentre

Gotsman[90]	Definite IE (Duke criteria[3])	100	Mean age 55 y ± 20 y (range 1–97 y) 55% male 23% PVIE	Retrospective, single centre
Griffin[197]	Definite, probable, and possible IE (von Reyn criteria[4]) in defined area of residence	78	Mean age 58 y (range 0–90 y) 58% male 14% CHD 5% PVIE	Retrospective, multicentre
Grossman[146]	IE, criteria: (1) At least 2 separate positive blood cultures from patients with known underlying heart disease and negative blood cultures in patients with known underlying heart disease, together with fever (>38°C) and new regurgitant heart murmur or embolic phenomena, or (2) histological evidence of infected endocardial vegetations in tissue obtained during open-heart surgery or autopsy	213	64% male 17% CHD	Retrospective, single centre
Gupta[128]	Definite IE (modified Duke criteria[1])in adult patients (>18 y)	83	Mean age 49 y ± 14 y (range 19–84 y) 77% male 31% PVIE 23% CHD 1% IVDU	Retrospective, single centre
Gupta[140]	Definite IE (modified Duke criteria[1])	109	Mean age 33 y ± 17 y (range 2–70 y) 75% male 32% CHD 10% PVIE	Retrospective, single centre

Habib[279]	IE (pathologic confirmation by surgical intervention)	93	Age not mentioned, no ratio of males:females mentioned, 32% PVIE	Retrospective, single centre
Haddy[55]	IE, criteria: (1) Autopsy evidence of IE, or (2) a compatible clinical history and 2 positive blood cultures prior to the initiation of adequate therapy or, where less than 4 cultures were taken, only 1 positive culture for *Streptococcus viridans* (alpha-haemolytic streptococcus), *Staphylococcus aureus*, or *Streptococcus pneumoniae*, or (3) a compatible clinical history with evidence of macro- or microembolism (petechiae, Osler's nodes, Roth's spots), the demonstrated absence of other diseases that might produce the clinical picture (i.e. pneumonia, renal infection, systemic lupus erythematosus, blood dyscrasia), and a response to what would be considered an adequate regimen of therapy	66	Mean age 44 y (range 6–83 y) 64% male 23% IVDU	Retrospective, single centre
Hajihossainlou[253]	Definite or possible IE (Duke criteria[3]) in discharge or postmortem diagnosis	286	Mean age 30 y ± 16 y (range 3–81 y) 60% male 9% CHD 14% PVIE 27% IVDU	Retrospective, multicentre
Hammel[56]	IE (criteria not clearly indicated)	31	Mean age 39 y (range 12–68 y) 74% male 3% IVDU 6% PVIE	Single centre, not indicated whether prospective or retrospective

Hayes[274]	Patients with PS from the First Natural History Study of Congenital Heart Defects (NHS-1)	464	Median age 30 y (range 18–77 y) 50% male 100% CHD	Prospective cohort study, multicentre
Heiro[211]	IE (Duke criteria[3]) patients who survived >1 y after the initial admission for IE	226	Mean age 52 y ± 17 y (range 18–87 y) 72% male 24% PVIE 4% CHD 8% IVDU	Retrospective, single centre
Heiro[210]	IE (Duke criteria)[3]) in adults	303	Mean age 54 y ± 17 y 72% male 3% CHD 8% IVDU 21% PVIE	Retrospective, single centre
Hill[102]	Definite IE (modified Duke criteria[1]) in patients >16 y	203	Median age 67 y (IQR 54–73 y) 60% male 34% PVIE 1% IVDU	Prospective observational cohort study, single centre
Hodes[148]	Cases of IE (criteria not clearly indicated)	47	Mean age 20.5 y 68% male	Retrospective, single centre
Hoen[244]	Definite IE (Duke criteria[3])	390	Mean age 60 y ± 17 y (range 16–95 y) 71% male 16% PVIE 1% CHD 5% IVDU	Retrospective population based survey, multicentre
Hogevik[65]	IE (modified von Reyn criteria[4]): Modification was detection of vegetation by sonography as an alternative to embolisation, retrospectively included were patients	90	Mean age 62 y (range 8–88 y) 46% male 10% CHD 15% PVIE 7% IVDU	Prospective non-randomised, single centre

	with IE identified at autopsy or by ICD 9 code			
Hsu[100]	Definite or possible IE (modified Duke criteria[1])	315	Mean age 51 y ± 22 y (range 0–92 y) 59% male 11% CHD 8% PVIE 4% IVDU	Retrospective review, single centre
Iga[183]	NVIE (criteria not clearly indicated)	32	Mean age 52 y (range 27–74 y) 78% male 19% CHD 0% IVDU	Retrospective, single centre
Jaffe[64]	Discharge diagnosis of IE, criteria: (1) At surgery or autopsy, valvular vegetations or embolic material, or both, were present with histologic or bacteriologic evidence of active infection (2) Two or more positive sets of blood cultures in the presence of a new regurgitant murmur or systemic embolism (3) When 2 of the following conditions were present: fever >38.5°C, new regurgitant murmur, embolic phenomenon	70	Mean age 47 y ± 19 y (range 15–88 y) 57% male 29% IVDU 16% PVIE 6% CHD	Retrospective review, single centre
Jain[188]	Definite IE (modified Duke criteria[1])	75	Mean age 27 ± 17 y (range 0–80 y) 69% male 0% IVDU 35% CHD 9% PVIE	Prospective observational, single centre
Jain[101]	Definite or possible IE (modified Duke criteria[1])	238	71% male 74% IVDU	Retrospective, single centre

Jalal[203]	IE, criteria: (1) Two or more positive blood cultures showing growth of the same microorganism, or (2) demonstration of vegetation on echocardiography in association with fever, evidence of vascular/immunologic phenomena, changing/new murmur, or worsening of heart failure	466	Mean age 23 y (range 0–60 y) 59% male 23% CHD 1% PVIE	Retrospective, single centre
Kahveci[214]	Definite aortic valve NVIE (modified Duke criteria[1])	51	Median age 39 y (range 9–75 y) 86% male 0% IVDU 0% PVIE	Retrospective, single centre
Keane[143]	Patients with AS from the Natural History Study of Congenital Heart Defects (NHS-1 and NHS-2)	462		Prospective cohort study, multicentre
Khaled[114]	Discharge diagnosis of IE (modified Duke criteria[1] with an additional minor criterion, namely increased erythrocyte sedimentation rate)		Mean age 29 y ± 15 y (range 12–60 y) 42% male 3% PVIE	Prospective, single centre
Khanal[185]	Definite IE (Duke criteria[3])	46	Median age 26 y (range 2–73 y) 57% male 9% CHD 2% PVIE	
Kim[62]	IE (von Reyn criteria[4])	55	Mean age 52 y (range 19–83 y) 71% male 16% CHD 23% PVIE 7% IVDU	Retrospective, single centre
Kim[239]	Echocardiographically diagnosed primary MVP	229	Mean age 51 y (range 14–88 y) 47% male	Prospective, single centre

King[60]	IE, criteria: Definite: Culture or Gram stain evidence of organisms on valvular tissue or peripheral embolus obtained at surgery or autopsy Probable: 100% of either 2 or 3 blood cultures or ≥72% of 4 or more cultures positive for the same organism plus evidence of a new regurgitant murmur or an intracardiac defect in a febrile patient Possible: One of only 2 blood cultures positive, plus fever and an intracardiac defect or embolic lesions, or 3 positive blood cultures in a patient with a valvular prosthesis and fever, or negative cultures in a persistently febrile patient with no explanatory diagnosis plus an intracardiac defect or valvular prosthesis	75	Mean age 48 y ± 18 y (range 15–90 y) 56% male 21% PVIE 18% IVDU	Prospective, multicentre
Kiwan[201]	IE, criteria: (1) Strong clinical evidence of the disease (2) Cardiac lesions or murmurs (3) Positive microbiological reports and or (4) Echocardiographic lesions	60	Mean age 28 y 67% male 7% PVIE 13% CHD	Prospective, single centre
Knudsen[247]	IE (modified Duke criteria[1])	172	19% PVIE 2% CHD 4% IVDU	Prospective, single centre
Knudsen[124]	Definite or possible IE (modified Duke criteria[1])	147	Mean age 65 y ± 14 y 62% male 29% PVIE 3% IVDU	Prospective, single centre
Knudsen[125]	Definite or possible IE (modified Duke criteria[1])	145	Mean age 65 y ± 14 y 60% male 26% PVIE	Prospective, single centre

			3% IVDU	
Koeda[130]	Definite IE (Duke criteria [3]) in adult patients (≥20 y)		Mean age 58 y ± 16 y 60% male	Retrospective, single centre
Koegelenberg[9,92]	Definite IE (Duke criteria[3])	47	Mean age 38 y ± 13 y 62% male 17% PVIE 6% CHD 0% IVDU	Prospective observational study, single centre
Korem[134]	Definite NVIE (modified Duke criteria[1]) in adults	37	Mean age 64 y ± 15 y 0% PVIE	Prospective observational study, single centre
Lamas[79]	NVIE (pathologically proven, and Duke criteria[3])	100	80% male 0% PVIE 6% IVDU	Prospective, single centre
Lamas[204]	IE (Duke criteria[3]) on BAV with modifications of the criteria: following additional minor criteria: the presence of newly diagnosed clubbing, splenomegaly, splinter haemorrhages, and petechiae; a high erythrocyte sedimentation rate; a high C-reactive protein level; and the presence of central non-feeding lines, peripheral lines, and microscopic haematuria	408	Study only reports on subsets	Retrospective, single centre
Leone[122]	Definite or possible NVIE (modified Duke criteria[1])	753	Mean age 62 y (range 4–95 y) 71% male 12% IVDU 9% CHD 0% PVIE	Prospective, multicentre
Li[215]	Surgically treated definite or possible IE (modified Duke criteria[1])	220	Mean age 39 y ± 14 y (range 3–75 y) 71% male 33% CHD	Retrospective, single centre

Loupa[245]	Definite or possible IE (Duke criteria[3], in case of pacemaker IE modified by Klug et al.[283])	101	Mean age 54 y ± 17 y (range 17–86 y) 70% male 31% PVIE 3% IVDU	Prospective, multicentre
Lowes[53]	IE (criteria not specified)	60	60% male 22% CHD	Retrospective survey, single centre
Lu[217]	Definite IE (modified Duke criteria[1]) in adults	148	Mean age 57 y ± 17 y 66% male 12% IVDU	Retrospective observational study, single centre
Ma[166]	Definite IE (modified Duke criteria[1]) in patients ≥18 y	115	Mean age 46 y ± 15 y 71% male 10% PVIE 24% CHD	Single centre
MacMahon[224]	IE, criteria: Evidence of cardiac involvement such as echocardiographically defined valvular vegetations or a murmur, with a positive blood culture on 2 or more occasions or histologic evidence of valvular vegetations, together with other evidence of infection such as pyrexia or elevated circulating immune complexes and evidence of the peripheral stigmata of IE such as embolic phenomena or splenomegaly. MVP diagnosis with Hickey definition[284]	136	Only subgroups presented	Prospective matched case-control study, multicentre
Manford[184]	IE (criteria not defined) with positive blood cultures	31	Mean age 58 y ± 18 y (range 23–85 y) 58% male 32% PVIE 6% IVDU 3% CHD	Retrospective, single centre

Mansur[149]	IE, criteria: Clinical presentation consistent with diagnosis and causative microorganism isolated in at least 2 blood cultures	287	Mean age 31 y ± 16 y (range 0.2–78 y) 64% male 12% CHD 23% PVIE 8% IVDU	Retrospective, single centre
Marks[238]	MVP (defined as systolic displacement into the left atrium of one or both leaflets beyond the plane of the mitral annulus in the parasternal long-axis view)	456	Only subgroups presented	Retrospective, single centre
Marks[164]	IE (modified Duke criteria[1]) in patients ≥18 y referred for surgical management	336	Median age 52 y (IQR 41–67 y) 75% male 8% IVDU 18% CHD 21%	Retrospective observational cohort study, single centre
Math[248]	Definite IE (modified Duke criteria[1])	104	Mean age 24 y (IQR 9–38 y) 71% male 39% CHD 20% PVIE	Prospective observational study, single centre
McKay[158]	IE (criteria not defined) patients undergoing cardiac surgery (excluding homografts)	29	Mean age 55 y (range 31–79 y) 66% male 6% PVIE	Retrospective, multicentre
Michelena[205]	Echocardiographically diagnosed BAV with no cardiovascular symptoms at diagnosis and with normal function or minimal dysfunction of the aortic valve, based on clinical evaluation confirmed by echocardiography showing no or at most mild stenosis (wide systolic valvular opening with mean gradient <20 mmHg in patients who underwent continuous wave Doppler) and no or mild regurgitation (no or mild left ventricular	212	Mean age 32 y ± 20 y 65% male	Prospective, multicentre

	enlargement, no or mild regurgitation by pulsed-wave of LVOT and of aortic arch or by colour flow Doppler) and with left ventricular ejection fraction ≥50%			
Michelena[206] [207]	Definite BAV of any type	416	Mean age 35 y ± 21 y 69% male	Retrospective cohort study, multicentre
Mills[193]	Non-stenotic BAV	41	Age range at follow-up 6–71 y 68% male	Prospective, single centre
Mills[227]	Mid-systolic click or late systolic murmur (or both) documented phonocardiographically	53	64% male	Retrospective, single centre
Mirabel[129]	Definite IE (modified Duke criteria[1]) in patients ≥18 y	51	Median age 52 y (IQR 33–70 y) 61% male 26% PVIE 12% CHD	Retrospective, single centre
Mokhles[111] (subgroup of Mokhles[115])	Adult patients who underwent surgery for definite IE (modified Duke criteria[1])	138	Mean age 54 y ± 14 y 77% male 12% CHD 1% IVDU 18% PVIE	Retrospective observational cohort study, single centre
Mokhles[115]	Definitive IE (modified Duke criteria[1]) in adult patients	191	Mean age 55 y 72% male 13% CHD 1% IVDU 21% PVIE	Retrospective observational cohort study, single centre
Mouly[82]	IE (Duke criteria[3]) in patients ≥15 y	89	Median age 60 y 66% male 8% IVDU 24% PVIE	Retrospective observational, single centre
Moura[94]	NVIE (Duke criteria[3])	69	Mean age 56 y ± 15 y 65% male 46% PVIE	Retrospective, single centre

			10% IVDU 15% CHD	
Murdoch[105]	Definite IE (modified Duke criteria[1]) in patients ≥18 y	2781	Mean age 57 y (IQR 43.2–71.8) 68% male 10% IVDU 23% PVIE	Prospective cohort study, multicentre (ICE-PCS)
Naggar[235]	Echocardiographically diagnosed MVP (Popp[259]) in patients aged 60 y or older	145	49% male	Retrospective, single centre
Nakagawa[251]	Definite or probable IE (modified Duke criteria[1])	118	Mean age 58 y (range 16–82 y) 58% male 0% IVDU 8% CHD 13% PVIE	Retrospective, single centre
Nakatani[163]	IE (Duke criteria[3])	513	Mean age 60 y ± 18 y (range 1–97 y) 62% male 2% IVDU	Prospective survey, multicentre
Nashmi[99]	Definitive IE (modified Duke criteria[1])	47	Mean age 32 y ± 20 y (range 0.4–78 y) 61% male 21% CHD 4% IVDU 21% PVIE	Retrospective, single centre
Netzer[88] (same data set as Netzer[153], longer follow-up)	IE (Duke criteria[3])	212	Mean age 53 y (range 17–90 y) 75% male 4% CHD 17% PVIE 10% IVDU	Retrospective review of clinical records, single centre
Netzer[153] (same data set as Netzer[88], shorter follow-up)	Definite or possible IE (Duke criteria[3])	212	75% male 4% CHD 17% PVIE 10% IVDU	Retrospective, single centre

Nishimura[229]	Echocardiographically diagnosed MVP with an age between 10 and70 y and no associated congenital anomalies or other valvular diseases, NYHA III-IV or diastolic dimension of >70 mm at the onset of the study	237	Mean age 44 y (range 10–69 y) 40% male	Prospective, single centre
Nissen[66]	NVIE, criteria: Definite IE: Positive histopathological evidence of IE by autopsy or cardiac surgery. Probable IE: Cases with a documentation of positive blood cultures, fever, and either cardiac murmurs or echocardiographic signs of IE	132	53% male 5% CHD 0% PVIE	Retrospective, multicentre
Nomura[120]	Definite or probable IE (modified Duke criteria[1])	62	Mean age 67 y ± 15 y 56% male 19% PVIE 8% CHD	Retrospective, single centre
Nunes[116]	Definite or possible IE (modified Duke criteria[1])	62	Mean age 45 ± 17 y (range 15–76 y) 63% male 8% IVDU	Prospective, single centre
Olmos[137]	Definite and possible IE (Duke criteria[3] until 2002, and modified Duke criteria[1] thereafter)	1122	Mean age 64 y ± 22 y Median age 62 y (IQR 47–72) 68% male 6% IVDU	Prospective, multicentre
Pachirat[86]	IE (Duke criteria[3])	160	Mean age 39 y ± 16 y 66% male 5% PVIE	Single centre, combined retrospective and prospective data collection
Pazdernik[109]	Definite IE (modified Duke criteria[1])	106	Mean age 57 y ± 15 y 80% male	Retrospective, single centre

			18% PVIE 1% IVDU	
Peat[236]	IE (von Reyn criteria[4])	78	Mean age 50 y ± 26 y 54% male 21% PVIE	Retrospective, single centre
Pedersen[51]	(1) Endocarditis at autopsy (2) Fever, heart murmur, at least 1 positive blood culture and absence of other diseases that might produce the observed clinical picture (3) Fever, heart murmur, evidence of peripheral embolism, absence of other diseases that might produce the observed clinical picture, and adequate response to antibiotic therapy despite negative blood cultures (4) In all cases classified as acute bacterial endocarditis, the heart murmur was required to be definitely changing during the period of observation	80	Mean age 42–46 y 54% male 10% CHD	Retrospective, single centre
Pelletier[50]	Discharge diagnosis IE, criteria: (1) Definite IE: Histologic evidence of infected endocardial vegetation(s) from examination of tissue obtained from cardiac surgery, embolectomy, or autopsy (2) Probable IE: Either uniformly positive blood cultures with known underlying heart disease and evidence of emboli to the skin or viscera, or negative blood cultures in individuals with fever (>38°C), new regurgitant valvular heart murmurs, and embolic phenomena	125	73% male 15% IVDU	Retrospective review of patient charts, multicentre

	(3) Possible IE: Either uniformly positive blood cultures with known underlying heart disease or embolic phenomena, or negative blood cultures with fever, known underlying heart disease, and embolic episodes			
Poesen[127]	Probable or definite IE (modified Duke criteria[1])	83	Median age 72 y (IQR 59–81 y) 66% male 8% PVIE 6% CHD	Retrospective, single centre
Rehman[187]	IE (Duke criteria[3])	30	Mean age 24 y 70% male 23% CHD 3% PVIE	Prospective, single centre
Rizzi[133]	Possible or definite IE (modified Duke criteria[1])	1056 (NVIE)	Median age 65 y (IQR 50–64) 71% male 11% IVDU 0% PVIE 9% CHD	Retrospective analysis of a multicentre, prospective observational cohort study
Robbins[145]	IE in patients ≥65 y, criteria: (1) Discharge diagnosis of IE, or (2) autopsy-proven IE, or (3) persistently positive blood cultures without a known primary site of infection	56	Mean age 72 y (range 65–92 y) 64% male	Retrospective, single centre
Roberts[70]	Necropsy patients with IE with vegetations on the aortic valve	96	78% male 11% IVDU 22% PVIE	Retrospective, multicentre
Rognon[74]	IE (Duke criteria[3])	151 (NVIE)	Mean age 55 y (range 16–89 y) 70% male 0% PVIE 6% IVDU 14% CHD	Retrospective, multicentre
Roucaut[231]	IE (von Reyn criteria[4])	350		Retrospective, single centre

Rudolph[147]	IE (criteria not stated)	50	Mean age 44 y ± 13 y 78% male	Single centre, probably prospective
Sadaka[219]	Definite IE (Duke as reported in ESC guidelines[14])	50	Mean age 33 y ± 11 y (range 16–78 y) 58% male 26% IVDU 22% PVIE 8% CHD	Prospective, single centre
Sandre[75]	IE (Duke criteria[3] and von Reyn[4] criteria), IVDU and PVIE excluded	80	Mean age 49 y (range 17–87 y) 69% male 0% IVDU 0% PVIE 9% CHD	Retrospective review, single centre
Sawae[275]	IE (criteria not clearly indicated)	91	25% CHD	Retrospective, multicentre
Schon[67]	IE (criteria not indicated)	51	Mean age 46 y ± 11 y (range 15–78 y) 69% male 20% PVIE 2% IVDU	Retrospective, single centre
Scudeller[249]	IE (criteria not indicated)	254	Mean age 67 y ± 14 y 67% male 32% PVIE 2% IVDU	Prospective observational, multicentre
Selton-Suty[119]	Patients with diagnosis of definite IE, age ≥18 y in predefined regions in France	497	Mean age 62 y ± 16 y (range 18–96 y) 74% male 6% IVDU 21% PVIE	Prospective population-based observational study, multicentre
Selton-Suty[72] **(study data from Delahaye,**[71] **modified)**	IE (von Reyn criteria[4], modified with echocardiographic and macroscopic findings[71]), excluding prosthetic devices	297	65% male	Prospective, multicentre

Senthilkumar[2] [18]	IE (modified Duke criteria[1]) with referral to tertiary centre	116	Mean age 30 y ± 14 y 70% male 4% PVIE 10% CHD	Prospective, single centre
Servy[285]	Definite IE (modified Duke criteria[1]) among adults (≥18 y) living in the study area	497	73% male 6% IVDU 21% PVIE 4% CHD	Prospective, multicentre
Siddiq[240]	IE, criteria: (1) Histopathologic evidence of the disease; (2) multiple positive blood cultures in the absence of another known primary source of bacteremia, together with at least 2 of the following signs or symptoms—fever, new or changing murmur, newly developed splenomegaly, hypersensitivity, or microvascular phenomena (e.g. Janeway lesions, Osier nodes, Roth spots, and splinter haemorrhages); and (3) intermittently positive blood cultures, or negative blood cultures when cultures were first obtained only after empiric antibiotic therapy, with at least 3 signs or symptoms. For right-sided endocarditis, entry criteria included positive blood cultures plus vegetation that was visualised on echocardiography, or positive blood cultures plus fever, septic pulmonary emboli, or heart murmur	159	Mean age 46 y ± 19 y (range 12–97 y) 64% male 67% IVDU	Prospective, single centre

Simsek-Yavuz[138]	IE (modified Duke criteria[1]) in hospitalised patients >14 y	325	Mean age 47 y ± 17 y (range 14–90 y) 58% male 43% PVIE 1% IVDU 8% CHD	Prospective 102 cases (first 5 y) and retrospective 223 cases thereafter, single centre
Singham[179]	IE, criteria: (1) All patients with evidence of heart disease and a positive blood culture (2) Patients with evidence of heart disease and negative blood cultures but with evidence of embolic episodes, fever with splenomegaly, finger clubbing, Osler's nodes, splinter haemorrhages and microscopic haematuria	101	60% male 30% CHD 1% PVIE	Retrospective, single centre
Skehan[233]	IE (criteria not stated)	185	7% IVDU 10% PVIE	Prospective, multicentre
Steckelberg[61]	IE (modified von Reyn criteria[4]): (1) Histopathologic evidence of infective endocarditis; or (2) multiple positive blood cultures (at least 2 positive cultures within a 24-hour period and at least 66% of cultures positive before initiation of antibiotics) with the same microorganism without another known primary source of bacteremia, and at least 2 of the following stigmata of infective endo-carditis: (a) fever, (b) new or changing cardiac murmur, (c) newly developed splenomegaly, (d) hypersensitivity or microvascular phenomena (e.g. Janeway	697		Retrospective from prospectively collected records, multicentre (comparison of a population- based cohort vs. cohort of Mayo Clinic)

	lesions, Osler nodes, Roth spots, conjunctival petechiae), or (e) emboli; or (3) intermittently positive blood cultures or negative blood cultures first obtained after administration of empiric antimicrobial therapy, together with at least 3 stigmata of infective endocarditis			
Strom[9]	Community-acquired IE (as assessed by study authors, criteria not indicated), IVDU excluded. Community-matched controls	273	Mean age 59 y ± 17 y 0% IVDU 10% CHD	Population-based, case-control study, multicentre
Sun[252]	IE (criteria not indicated), excluding PVIE and devices		Mean age 48.6 y 61% male 0% PVIE	Retrospective, single centre
Suzuki[212]	Cardiac surgery for IE (criteria not stated)	27	26% CHD	Retrospective, single centre
Tariq[159]	IE (modified Duke criteria[1])	66	Mean age 29 y 67% male 50% CHD 2% IVDU 8% PVIE	Retrospective, single centre
Tariq[157]	IE (modified Duke criteria[1])	159	Mean age 35 y ± 21 y 65% male 25% CHD 1% IVDU 5% PVIE	Retrospective, single centre
Terpenning[59]	Definite or probable bacterial IE (von Reyn[4] criteria, Pelletier criteria[50])	144	23% IVDU	Retrospective review of patient charts, multicentre
Thamlikitkul[150]	IE in patients ≥13 y, criteria (modified from Von Reyn[4]): Positive blood culture for the same microorganism on at least 2 specimens plus	105	Mean age 32 y 71% male 29% IVDU	Retrospective, single centre

	(1) pathological evidence of infective endocarditis at autopsy or operation, or (2) cardiac vegetation detected by echocardiography, or (3) presence of heart disease and/or history of intravenous drug abuse with embolic phenomena or with unidentified foci of bacteremia			
Thell[144]	Pathologic samples (autopsy and excision) of valves with IE diagnosis in patients >60 y	42	69% male 5% PVIE	Retrospective (pathology samples), multicentre
Tleyjeh[87]	IE (modified Duke criteria [1]) in adults ≥18 y	102	Mean age 62 y (range 19–91 y) 72% male 21% PVIE 3% IVDU 7% CHD	Retrospective (population-based survey), multicentre
Todd[48]	TTE studies with primary indication of IE diagnosis, TTE or TOE suggesting IE diagnosis	29		Retrospective, single centre
Tornos[73]	NVIE in non-IVDU, criteria for IE: (1) Clinical findings consistent with infective endocarditis, including at least 2 of the following signs: fever, heart murmur, emboli, splenomegaly, and microvascular phenomena; (2) 2 or more blood cultures positive for the same microorganism; and (3) histopathological evidence of valvular infection at necropsy or operation	194	Median age 50 y (range 7–82 y) 66% male 0% IVDU 0% PVIE 10% CHD	Prospective observational, single centre
Tran[208]	IE (Duke criteria[3])	132	Mean age 54 y (range 19–83 y) 61% male 22% PVIE 13% IVDU	Retrospective, single centre

			11% CHD	
Tresch[230]	Echocardiographically diagnosed MVP in patients >60 y	40		Single centre
Tribouilloy[216]	Definite IE (Duke criteria)[3]) with native aortic valve involvement	310	Mean age 59 y ± 15 y 82% male 0% PVIE	Prospective, observational, multicentre
Tugcu[110]	Possible or definite IE (modified Duke criteria[1])	28 (NVIE)	Mean age 46 y (range 16—88 y) 68% male 0% PVIE 7% CHD	Retrospective review, single centre
Turak[135]	Definite IE (modified Duke criteria[1]) in adults	121	Mean age 55 y ± 14 y 53% male 42% PVIE 6% CHD	Retrospective, single centre
Tzemos[209]	BAV on transthoracic echocardiography and absence of complex congenital cardiac defects	642	Mean age 35 y ± 16 y 68% male	Retrospective, single centre
Van der Meer[8]	IE (von Reyn criteria[4])	349 (NVIE)	Median age 47 y (range 2—89 y) 61% male 11% CHD 0% PVIE 0% IVDU	Prospective epidemiologic study, multicentre
Varstela[63]	Patients with aortic valve surgery for IE	58	Mean age 47 y (range 19—71 y) 88% male	Retrospective, single centre
Venezio[57]	(1) Typical histopathology found at surgery or autopsy; or (2) 3 or more positive blood cultures plus at least 2 of the following: fever, heart murmur, systemic embolisation or biopsy-proved vasculitic skin lesions, and	37		Retrospective, single centre

	echocardiographic evidence of a valvular vegetation			
Vered[234]	Patients with echocardiographically diagnosed MVP	42		Retrospective, single centre
Verheugt[141]	Patients with CHD ≥18 y, included in CONCOR registry[286] IE (modified Duke criteria[1])	10210	49% male 100% CHD	Prospective cohort study, multicentre
Verheul[276]	NVIE (von Reyn criteria[4])	141	Mean age 45 y (range 18—77 y) 74% male	Retrospective, single centre
Vlessis[202]	IE (modified[69] von Reyn criteria[4])	140	Mean age 57 y ± 3 y 65% male 11% IVDU 22% PVIE 4% CHD	Retrospective, single centre
Walls[106]	IE patients (modified Duke criteria[1]) in ICE-PCS cohort[105] from New Zealand	336	Median age 60 y (range 15—98 y) 68% male 31% PVIE 13% CHD 5% IVDU	Prospective cohort (ICE-PCS cohort study[105]), multicentre
Watanakunakorn[69]	IE (modified Steckelberg criteria[61])	204	Median age 60–70 y (range 0—91 y) 56% male 16% IVDU 14% PVIE 4% CHD	Retrospective 1980–1985, prospective 1986–1990, single centre
Watt[255]	IE in patients ≥16 y (modified Duke criteria[1])	132	Median age 47 y (range 16–85 y) 69% male 10% PVIE 8% CHD	Prospective observational, multicentre
Weinberger[23]	NVIE (von Reyn criteria[4])	135	Mean age 60 y (range 18–85 y)	Retrospective, single centre

			63% male 0% PVIE (excluded) 11% CHD 1% IVDU	
Wells[237]	IE in patients ≥15 y (von Reyn criteria[4])	98	Mean age 52 y ± 20 y 64% male 8% PVIE 3% CHD 4% IVDU	Retrospective, single centre
Welton[54]	(1) Persistent bacteremia proved by 2 or more blood cultures separated by an interval of 12 to 24 hours demonstrating the same organism with concomitant clinical features of endocarditis consisting of fever, cardiac murmur, and, frequently, 1 or more of the following: systemic emboli, splenomegaly, haematuria or echocardiographic valvular vegetations (2) Pathologic confirmation of endocarditis at surgery or autopsy and a preceding clinical course consistent with infective endocarditis	117	Mean age 36 y 29% IVDU 3% CHD 3% PVIE	Retrospective, single centre
Weng[78]	IE (Duke criteria[3])	109	Mean age 38 y (range 8–78 y) 73% male 14% CHD 5% IVDU 25% PVIE	Retrospective, single centre
Werner[76]	IE (Duke criteria[3])	104	Median age 59 y 26% PVIE	Retrospective, single centre
Wong[113]	Definite or possible IE (modified Duke criteria[1])	47	Mean age 66 y (range 16–93 y) 77% male 28% PVIE	Retrospective review, single centre

			4% CHD	
Woo[198]	Primary referrals with IE (diagnostic criteria not specified)	176	Mean age 30 y ± 13 y 48% male 5% PVIE 22% CHD 3% IVDU	Mixed retrospective and prospective, single centre
Wu[123]	Definite IE in patients ≥18 y (modified Duke criteria[1])	192	Median age 50 y (range 19–92 y) 75% male 29.5% IVDU 9% PVIE	Retrospective, single centre
Yeo[241]	Echocardiographically diagnosed MVP (Feigenbaum[287])	98	Mean age 42 y ± 17 y 55% male	Retrospective, single centre
Yiu[246]	Community-acquired IE (modified Duke criteria[1]) in adults	172	Mean age 52 y ± 17 y 66% male 30% IVDU 9% CHD	Retrospective cohort, single centre
Yoshinaga[95]	IE (modified Duke criteria[1])	239	Median age 12 y (range 1–62 y) 90% CHD	Retrospective observational cohort study, multicentre (66 institutes)
Yousuf[97]	IE (Duke criteria[3])	45	Mean age 31.9 y 98% male 86.7% IVDU	Retrospective analysis of case records, single centre
Zuppiroli[226]	Patients with MVP referred for evaluation	275	Mean age 43 ± 19 y 47% men	Prospective observational, single centre
Zuppiroli[288]	Patients with MVP (echocardiographically diagnosed)	316	Mean age 42 ± 15 y 30% male	Prospective observational, single centre

Table 28 – Inclusion criteria, population data, and designs of included studies

2D: two-dimensional; AS: aortic valve stenosis; BAV: bicuspid aortic valve; CHD: congenital heart disease; ESC: European Society of Cardiology; ICE: International Collaboration on Endocarditis; ICE-PCS: International Collaboration on Endocarditis-Prospective Cohort Study; ICD: International Statistical Classification of Diseases and Related Health Problems; IE: infective endocarditis; IQR: interquartile range; IVDU: intravenous drug user; LSIE: left-sided infective endocarditis; LVOT: left ventricular outflow tract; MVP: mitral valve prolapse; NVIE: native valve infective endocarditis; NYHA: New York Heart Association; PS: pulmonary valve stenosis; PVIE: prosthetic valve infective endocarditis; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography