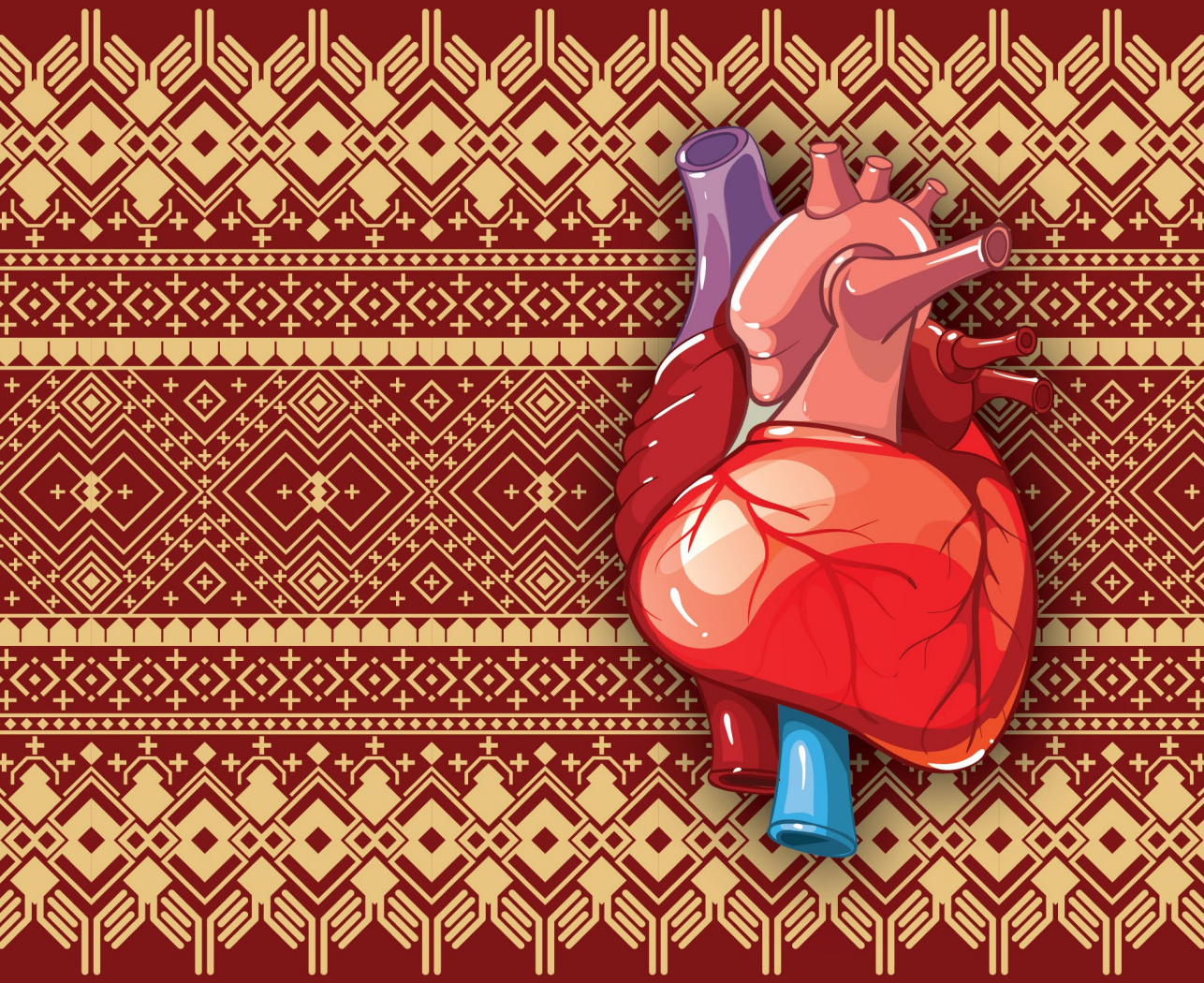
# Management of Rheumatic Heart Disease in Low and Middle Income Countries Focus on Indonesia



Ade Meidian Ambari

Management of Rheumatic Heart Disease in Low and Middle Income Countries Focus on Indonesia

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# Management of Rheumatic Heart Disease in Low and Middle Income Countries Focus on Indonesia

**Management van reumatische hartziekte in lage- en middeninkomenslanden Focus op Indonesië**

(met een samenvatting in het Nederlands)

**Tata laksana penyakit jantung rematik di negara berpendapatan rendah dan menengah Fokus di Indonesia**

(with summary in Bahasa)

## Proefschrift

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**Ade Meidian Ambari**

geboren op 20 mei 1977
te Banding Agung, Sumatra Selatan, Indonesië

**Promotoren:**

Prof. dr. P.A.F.M. Doevendans
Prof. dr. Budhi Setianto

**Copromotoren:**

Dr. M.J. Cramer
Dr. dr. Anwar Santoso

**Beoordelingscommissie:**

Prof. dr. D.P.V. de Kleijn
Prof. dr. S.A.J. Chamuleau
Prof. dr. M.C. Post
Prof. dr. ir. H.M. den Ruijter
Prof. dr. Bambang Budi Siswanto

# Content

## ABBREVIATIONS

| | |
|---|---|
| 6MWD | 6 Minutes Walking Distance |
| 6MWT | 6 Minutes Walking Test |
| ACEI | Angiotensin Converting Enzyme Inhibitor |
| AF | Atrial Fibrillation |
| APC | Antigen Presenting Cell |
| AR | Aorta Regurgitation |
| ARF | Acute Rheumatic Fever |
| ASO | Anti-streptolysin-O |
| AT | Angiotensin |
| BHS | Beta Hemolytic Streptococcus |
| BMI | Body Mass Index |
| BPG | Benzathine Penicillin G |
| CABG | Coronary Artery Bypass Grafting |
| CAD | Coronary Artery Disease |
| CD4+ | Cluster of differentiation 4 |
| CI | Confidence Interval |
| c-Myc | Cellular Myc |
| CPET | Cardiopulmonary Exercise Test |
| CR | Cardiac Rehabilitation |
| CTGF | Connective Tissue Growth Factor |
| CVA | Cerebrovascular Attack |
| DAB | Diaminobenzidine |
| DBP | Diastolic Blood Pressure |
| DC | Dendritic Cell |
| DM | Diabetes Mellitus |
| DNA | Deoxyribonucleic Acid |

| | |
|---|---|
| ECG | Electrocardiogram |
| ECM | Extracellular Matrix |
| EGF | Epidermal Growth Factor |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| ERK | Extracellular Signal-Regulated Kinase |
| ESC | European Society of Cardiology |
| ESR | Erythrocyte Sedimentation Rate |
| FcR | Fc Receptor |
| FOXP3 | Forkhead Box P3 |
| GAS | Group A Streptococcus |
| GDP | Guanine Diphosphate |
| GTP | Guanine Triphosphate |
| GlcNAc | N-Acetylglucosamine |
| HDL | High-Density Lipoprotein |
| HLA | Human Leucocyte Antigen |
| HR | Hazard Ratio |
| IARK | Interleukin Associated Receptor Kinase |
| IFN | Interferon |
| IgG | Immunoglobulin G |
| IHC | Immunohistochemistry |
| IL | Interleukin |
| INR | International Normalized Ratio |
| JNK | Jun N-Terminal Kinase |
| LA | Left Atrium |
| LDL | Low-Density Lipoprotein |
| MAPKs | Mitogen Activated Protein Kinases |
| MCP | Monocyte Chemoattractant |
| MMP | Matrix Metalloproteinase |
| MR | Mitral Regurgitation |
| mRNA | Messenger Ribonucleic Acid |
| MS | Mitral Stenosis |
| MVA | Mitral Valve Area |
| MVR | Mitral Valve Replace |
| MVr | Mitral Valve repair |

| | |
|---|---|
| MVS | Mitral Valve Surgery |
| MYD88 | Myeloid Differentiation 88 |
| NET | Neutrophil Extracellular Trap |
| NF-κB | Nuclear Factor Kappa Beta |
| NGF | Nerve Growth Factor |
| NIH | National Institute of Health |
| NT-proBNP | N-Terminal Pro Brain Natriuretic Peptide |
| NYHA | New York Heart Association |
| OR | Odd Ratio |
| PAI | Plasminogen Activator Inhibitor |
| PBMV | Percutaneous Balloon Mitral Valvuloplasty |
| PDGF | Platelet-derived Growth Factor |
| RAcP | Receptor Accessory Protein |
| RAS | Renin Angiotensin System |
| RHD | Rheumatic Heart Disease |
| RMS | Rheumatic Mitral Stenosis |
| SBP | Systolic Blood Pressure |
| SMAD | Suppressor of Mothers Against Decapentaplegic |
| sST2 | Soluble Suppression of Tumorigenesis-2 |
| TAPSE | Tricuspid Annular Plane Systolic Excursion |
| TEE | Trans-esophageal Echocardiography |
| TGF | Transforming Growth Factor |
| TIMP | Tissue Inhibitor Metalloproteinase |
| TLR | Toll-like Receptor |
| Th | T-helper |
| TNF | Tumor Necrosis Factor |
| TRA | Tricuspid Regurgitation Area |
| TRAF | Tumor Necrosis Factor Receptor Associated Factor |
| TTE | Trans Thoracal Echocardiography |
| VCAM-1 | Vascular Cell Adhesion Protein-1 |
| VO2 | Volume Oxygen |
| WHO | World Health Organization |

# Chapter 1

## General introduction and thesis outline

# INTRODUCTION

## Epidemiology of Rheumatic Heart Disease

Rheumatic heart disease (RHD) remains a global health burden. In 2017, approximately 38-40.8 million cases of RHD were observed all around the world. There is a significant gap in RHD prevalence between endemic and non-endemic regions. The prevalence of RHD in non-endemic regions is 3.4 cases per 100,000, whereas, in endemic regions, it is higher than 1,000 cases per 100,000. RHD is also responsible for the premature deaths of 0.15/100000 children and an annual case-fatality rate of 1.5% per year among the global population ages.[1,2] High mortality rate of RHD was also reported, with an average of 6% to 12% in highly endemic areas such as Ethiopia and Pakistan.[2] Migration has an influence on both the epidemiology and management of RHD. Even though RHD has been declared eliminated in developed nations, a recent screening of refugees in Italy found that 2.1% of them had subclinical RHD.[3]

**The situation in Indonesia**. No recent integrated national data regarding the prevalence and incidence of RHD are available. In 1995, RHD prevalence was estimated to be 0.3-0.8% for children aged 5-15.[4] Recent local reports are available from some parts of Indonesia, such as Papua, Bandung, and Jakarta. Eighty-three out of 15,608 mine workers in Papua suffered from RHD.[5] A cardiac center in Bandung observed that 108/4,682 (2.3%) of the patients were diagnosed with RHD. Meanwhile, the Cardiovascular Centre Harapan Kita, Jakarta, a national cardiovascular disease referral hospital in Indonesia, stated that 40.5% of 7112 valvular cases during 2016–2019 were RHD cases.[6,7]

## Rheumatic Heart Disease

Rheumatic heart disease (RHD) is an autoimmune sequelae of a mucosal infection by *Streptococcus pyogenes* (Group A Streptococcus, GAS). It is a chronic condition resulting from single to numerous episodes of acute rheumatic fever. B-cells and T-cells distinguish GAS antigens and self-antigens through the amino acid sequence and the structural conformation. The M protein is the antigenic structure of GAS that shares a similarity to a human protein. It has long α-helical coil that structure in several valvular proteins, cardiac

myosin and tropomyosin. There are four distinct part (A-D) which region A confer type- specific protection. It inhibits antibody binding, thus effectively camouflage the bacteria against immune system. Bacterial antigens also can imitate DNA, carbohydrates, and other protein, hence, inducing immunological cross-reactions through infection, autoimmune sequelae, and vaccination.[8,9,10]

## Pathophysiology of Rheumatic Heart Disease

The definitive pathophysiology of RHD is still unknown, but some ideas and hypotheses are trying to reveal the pathomechanism. Primarily, it is thought to be caused by immunological mimicry or cross-reactivity between the bacteria antigen and host proteins in genetically predisposed patients. It is suspected that the mutation of Fc receptor (FcR) genes play an important role in RHD. The humoral and cellular immune responses were induced following GAS infection at the pharynx. Most of the time, they do not trigger acute rheumatic fever directly but need several episodes that escalate immune response and cause tissue damage.[11]

As antigen-presenting cells, the macrophages and dendritic cells identify and process GAS resulting in B-cell formations. They eventually release TNF-α and IFN-γ, activate the monocytes, and increase the macrophages, IL-8, and IL-6, which further attract neutrophils.[12,13] Neutrophils phagocytes bacteria which then release the antigen to T cells. IgM and IgG will be produced, and CD4+ will be activated. It is consistent with the hypothesis that HLA class II (Human Leucocyte Antigen) is more closely associated with the elevated risk of ARF or RHD than class I.

The autoantibodies are distributed in the bloodstream and attached to the endothelium of cardiac valves. It increases the expression of Vascular Cell Adhesion Protein-1 (VCAM-1), which attracts T-cells to the subendothelial valve. Granulomatous inflammation following T-cell auto-reactivation resulted in the Aschoff body.[14] The chordae tendinae will elongate and swell, exposing the extracellular matrix with anti-collagen antibodies and covered with pro-inflammatory agents.[15] This disease renders the heart valves, particularly the mitral, vulnerable[16] **(Figure 1)**.

Fibrinoid degeneration, leucocytic infiltrates, Aschoff nodules, and calcification were seen in histopathological alterations in rheumatic mitral stenosis. Valvular calcium levels were elevated in older individuals, men, and those with significant mitral stenosis. The degree of inflammatory cellular infiltration was linked to valve calcification, fibrinoid degeneration to ARF, leucocytic infiltrates to a 10-year illness duration, and fibrosis to the absence of atrial fibrillation. C-reactive protein and anti-streptolysin titres were elevated in cells stained with CD20 and CD8.[17]

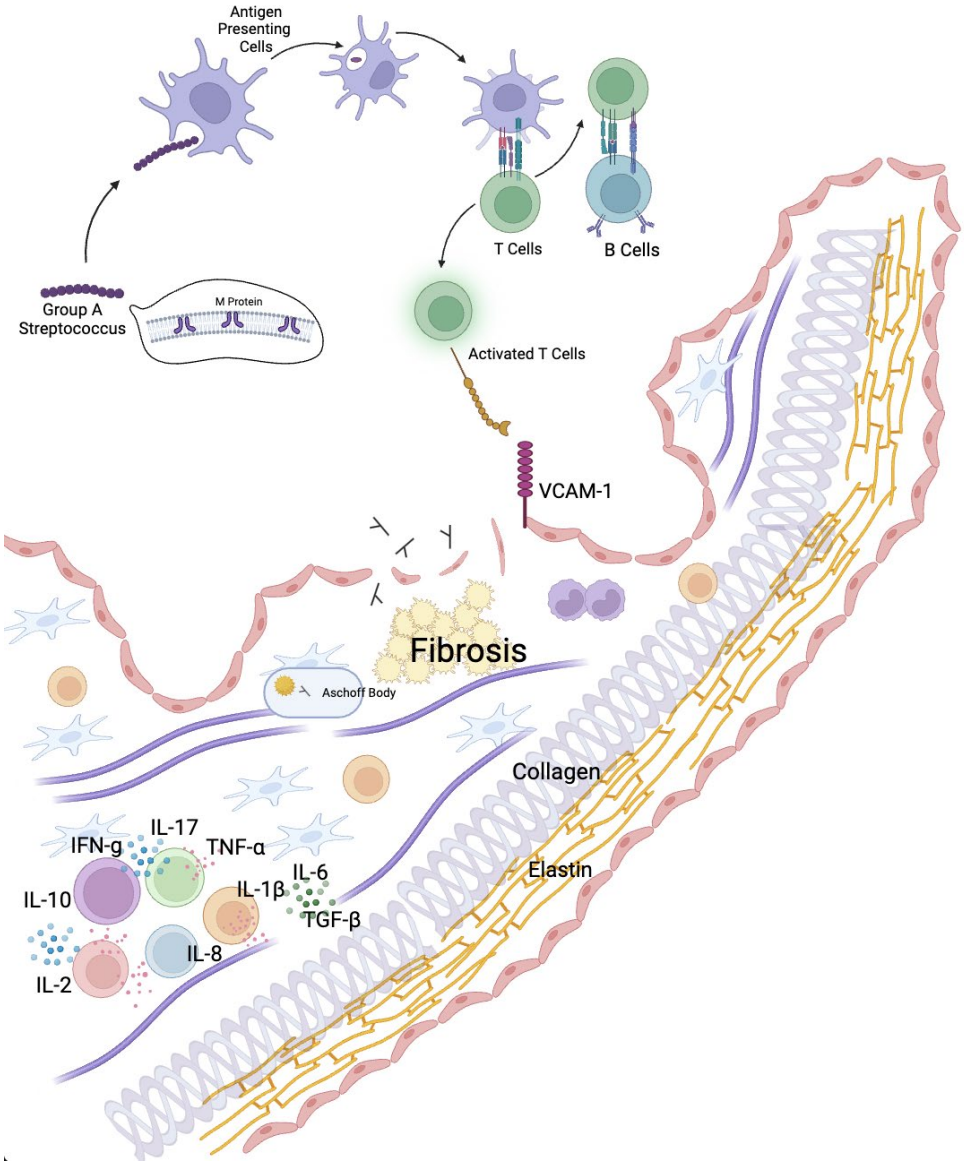


**Figure 1.** Pathophysiology of rheumatic heart disease. GAS invade the respiratory tract and followed by humoral and cellular immune response. APC which recognize GAS starting to form B-cells and activate T-cells. The autoantibodies which distributed in the bloodstream increase the expression of VCAM-1 and attract T-cells to subendothelial valve. This repeated inflammation process resulted in the Aschoff Body. The chordae tendinae will swell, elongate, forming the fibrosis and makes the valve vulnerable

## Rheumatic Heart Disease Diagnosis and Clinical Manifestations

Duckett Jones was the first to establish diagnostic criteria for RHD before the etiology and specific tests for RHD were known [Thomas Duckett Jones (February 2, 1899, Petersburg, Virginia – November 22, 1954, New York City) was an American physician, cardiologist, and leading expert on rheumatic fever and rheumatic heart disease]. Since then, Jones Criteria has been evolving to multiple modifications, although misdiagnosis is still possible.[18]

As Revised Jones Criteria mention, a patient needs two major or one major +2 minor signs to be diagnosed with initial ARF. Two major or one major +2 minor or three minor signs are considered to be recurrent ARF. The major criteria include carditis, chorea, erythema marginatum, subcutaneous nodules, and polyarthritis. In high risk population, monoarthritis and polyarthralgia are also considered as the major criteria. Meanwhile, minor criteria are fever (≥ 38.5 C), laboratory marker shows ESR > 60mm/h and/or CRP > 3.0 mg/dL, and ECG records that show AV block after considering the age variability.[19]

Echocardiography is the most accessible additional evaluation for diagnosing RHD and predicting its prognosis, as it looks for valve anomalies such as regurgitation, thickening, and specific shape. The World Heart Federation has echocardiography diagnostic criteria for RHD classified into two age groups (older or younger than 20 years old).[20]

**Table 1.** Diagnostic criteria for rheumatic heart disease

| Patient ≤ 20 years old | Patient ≥ 20 years old |
|---|---|
| **Definite RHD (1 criteria)** | **Definite RHD (1 criteria)** |
| Pathologic MR and at least two morphological features of RHD of mitral valve | |
| MS mean gradient ≥ 4 mmHg | |
| Pathologic AR and at least two morphological features of RHD of aortic valve | Pathologic AR and at least two morphological features of RHD of aortic valve, only in patient <35 years old |
| Borderline disease of aortic and mitral valve | Pathologic AR and at least two morphological features of RHD of mitral valve |

| |
|---|
| Borderline RHD (1 criteria) |
| At least two morphological features of RHD of mitral valve without pathological regurgitation or stenosis |
| Pathological MR |
| Pathological AR |
| Normal Echocardiography (4 criteria) |
| Physiological MR |
| Physiological AR |
| An isolated morphological feature of mitral valve (i.e valvular thickening) without any pathological regurgitation or stenosis |
| Morphological feature of aortic valve (i.e valvular thickening) without any pathological regurgitation or stenosis |

AR, aortic regurgitation; MS, mitral stenosis; RHD, rheumatic heart disease

Morphologic features due to Rheumatic Heart Disease:

| **Mitral** | **Aortic** |
|---|---|
| • Thickening of anterior leaflet of mitral valve ≥ 3mm<br>• Thickening of chordae<br>• Restricted leaflet motion<br>• Excessive motion of leaflet tip during systole | • Coaptation defect<br>• Prolapse<br>• Restricted leaflet motion<br>• Focal or irregular thickening |
| **Pathologic MR** | **Pathologic AR** |
| • Seen on two views<br>• In at least one view, jet length greater than or equal to 2 cm<br>• Velocity more than or equal to 3m/s<br>• Pansystolic jet in at least one envelope | • Seen on two views<br>• In at least one view jet length greater than or equal to 1cm<br>• Maximum speed more than or equal to 3m/s<br>• Pan-diastolic jet in at least one envelope |

RHD predominantly affects the left-sided valves, with the mitral valve suffering the most damage. Cardiac valve regurgitation is a symptom of acute rheumatic valvulitis; nevertheless, persistent inflammation and recurrent rheumatic infection can lead to stenosis over time. Acute mitral valvulitis is characterized by mitral regurgitation of any degree, mitral annular dilation, chordal elongation, anterior leaflet prolapses, and, rarely, chordal rupture.[1,20]

## Rheumatic Heart Disease Study in the Indonesian Population

Rudiktyo et al. conducted a study in Indonesia to investigate whether there is a relationship between rheumatic etiology and ventricular dysfunction in patients with chronic MR.[21] The study revealed that rheumatic etiology was linked to more severe impairment of the left ventricular function; however, there was no association between rheumatic etiology and reduced right ventricular systolic function in patients with significant chronic MR. The study also included patients with degenerative MR as a comparison group to distinguish the association between the rheumatic process and reduced ventricular function, independent of hemodynamic factors. The results indicated that rheumatic etiology was independently linked to more severe LV systolic function impairment, but not with RV systolic function. These findings suggest that, in addition to the chronic volume overload of the left ventricle, there may be another mechanism that aggravates the LV function in patients with rheumatic MR. The intrinsic myocardial process in RHD could play a role in the mechanism behind this impaired LV contractility.[21]

A study conducted on an Indonesian population examined various clinical and echocardiographic characteristics across multiple types of valvular lesions in RHD. Results indicated that isolated mitral stenosis was the most frequent form of valve lesions in RHD. Predominantly, female and younger patients were affected, and AF, reduced RV contractility, elevated pulmonary pressure, and preserved LVEF were common findings.[22]

Another study aimed to investigate the impact of aging on the progression of rheumatic MS in the Indonesian population by analyzing the association between age and different echocardiographic parameters in patients with isolated severe rheumatic severe MS. Age showed significant correlations with mean MVG, LA diameter, Wilkin's score, TR Vmax, TR maxPG, and TAPSE.[23]

Despite the lack of a nationwide RHD screening program in Indonesia, introducing a screening program targeting schoolchildren and siblings from where referral cases originated could be a practical approach to national RHD prophylaxis. Portable echocardiography is preferred for RHD screening in remote areas, but a simplified echocardiographic criterion without spectral Doppler evaluation is needed in selected regions.[24]

## Current Treatment in Rheumatic Heart Disease

There is currently no specific treatment for RHD, particularly valves. The valvular injury is irreversible. Secondary prevention is needed to avoid reinfection of Group A streptococcus with benzathine penicillin G every 3-4 weeks as prophylaxis.[25] ACE inhibitors, diuretics, beta-blockers, and digoxin may be administered to RHD patients with heart failure to reduce the symptoms prior to invasive treatments such as PBMV, open commissurotomy, valve repair, or replacement. Valve replacement is frequently selected over valve repair for severe RHD cases, despite the necessity for lifelong warfarin administration and INR monitoring.[26]

## Challenges of Current Treatments in RHD

Due to little awareness about 'strep throat' signs and symptoms, RHD is typically ignored. Mild symptoms, complaints that resolved within a few days, and a lack of information about acute rheumatic fever cause individuals to disregard and not fully treat it. After years, doctors subsequently diagnose many cases of severe rheumatic heart disease at a late stage. Meanwhile, consistency in administering Penicillin and monitoring becomes another RHD treatment challenge.[27] Some novel treatments are in ongoing trials and development; however, like ACEI, which is suggested to reduce valve fibrosis, there are opposing views that reject the treatment due to its hypotension effect.[28]

Therefore, we composed two main questions throughout this thesis:

1. What is a potential approach to managing RHD, especially RMS focusing on fibrosis attenuation?
2. Can we use angiotensin-converting inhibitor (ACEI) for RMS patients, and does it give clinical benefit to these patients?

## THESIS OUTLINE

This thesis has seven chapters that discuss RHD from the cellular aspect to the comprehensive management. **Chapter 1** contains introduction. **Chapter 2** explains how RHD would develop from recurrent inflammation and GAS antigen stimulation to progressive fibrosis of the heart valve and tissue. Angiotensin has been identified as a molecule contributing to heart valvular fibrosis. On the molecular level, IL-33/sST2 and TGF-β pathway induced by angiotensin produce growth factors, cytokines, and immune cells and cause cellular adhesion, fibroblast proliferation, and accumulation of extracellular matrix. As a well-established drug, ACE inhibitor is expected to be a solution to reduce fibrosis based on the explained mechanism above.

**Chapter 3** explores the search for a less expensive, equally effective alternative to invasive treatment. Each treatment has advantages and disadvantages. PBMV or MVR is still the preferred management solution for RMS. MVR can be performed on patients with more complex and severe conditions, but PBMV is less invasive and expensive than MVR.

**Chapter 4** discusses the next step of RMS treatment following MVR or PBMV and preparing the patient for reintegration into daily life, particularly for those who have undergone surgery. Phases I and II are conducted in the cardiac center hospital, while phase III is continued at home, starting with exercise capacity assessment and deciding the individual exercise prescription, having a multidisciplinary team assembled, and full support from family that can aid the patient to get a full recovery.

**Chapter 5** considers a non-invasive method of treating RMS patients as a strategy to reduce costs in low- to middle-income countries. According to the previous chapters on the cellular mechanism of RHD, ACE inhibitors

have emerged as a promising treatment for decreasing the morbidity and severity level of RMS patients, reducing the number of high-cost and high-risk operations. ACEI has anti-fibrotic and anti-remodeling effects in general. We are conducting a randomized clinical trial to determine the effect of Ramipril versus placebo on sST2 levels. According to the hypothesis, the ACEI will reduce sST2 and minimize the fibrosis process in the heart valve.

**Chapter 6** Since its inception, Penicillin has been a narrow-spectrum antibiotic for numerous diseases. We examined the significance of Penicillin as the main treatment for secondary prophylaxis using meta-analysis. As a preventative measure against GAS reinfection, Penicillin should be administered prior to the onset of the autoimmune response.

The last chapter, **chapter 7**, those topics are discussed comprehensively to provide clinical relevance and further directions.

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Chapter 2

# Angiotensin converting enzyme inhibitors (ACEIs) decrease the progression of cardiac fibrosis in rheumatic heart disease through the inhibition of IL-33/sST2.

Ade Meidian Ambari, Budhi Setianto, Anwar Santoso, Basuni Radi, Bambang Dwiputra, Eliana Susilowati, Fadilla Tulrahmi, Pieter A. Doevendans, Maarten-Jan Cramer

*Front Cardiovasc Med. 2020 Jul 28;7:115.*

## ABSTRACT

Rheumatic heart disease (RHD) is common in developing countries and poses a big medical challenge and burden. The pathogenesis of RHD is influenced by the triad of host, agent, and environment. Autoantigens generated from Group A Streptococcus (GAS) infection are captured by the resident dendritic cells (DCs) in the heart's valvular endothelium. DCs differentiate into antigen presenting cells (APC) in the valve interstices. APC induces activation of autoreactive T cells, which triggers inflammation and tissue fibrosis. Cardiac fibrosis is promoted through the activation of Mitogen activated protein kinases (MAPKs) and its downstream signaling, including its interaction with transforming growth factor-β (TGF-β) and Smad proteins. TGF-β-induced phosphorylation of Smad2 complexes with Smad3 and Smad4, and translocates into the nucleus. Angiotensin II enhances the migration, maturation, and presentation of DC. In RHD, Angiotensin II induces fibrosis via the stimulation of TGF-β, which further increases the binding of IL-33 to sST2 but not ST2L, resulting in the upregulation of Angiotensin II and progression of cardiac fibrosis. This cascade of inflammation and valvular fibrosis causes calcification and stiffening of the heart valves in RHD. Angiotensin converting enzyme inhibitors (ACEIs) inhibit Angiotensin II production, which in turn decreases TGF-β expression and the onset of overt inflammatory response. This condition leads to a reduction in the sST2 as the decoy receptor to "steal" IL-33, and IL-33 binds to ST2L and results in cardio-protection against cardiac fibrosis in the pathogenesis of RHD.

## INTRODUCTION

Rheumatic heart disease (RHD) is still prominent in developing countries and poses a big medical challenge and burden, especially among the youth.[1] The incidences of RHD is estimated to be between 15.6 and 19.6 million cases worldwide, and it accounts for 350,000 deaths each year.[2] Its morbidity increases the number of "disability-adjusted life-years lost" to 5.2 million per year, globally.[3] RHD varies demographically. Prevalence in Africa was reported to be between 5 and 7 per 1,000 children aged 5 and 14 years in 2005.[4] In New Zealand, prevalence of RHD varied from 5 to 51 per 100,000 individuals, and 80–254 per 100,000 in Australia.[5] In South and Central America, RHD affects 1–3 per 1,000 school children. India has the highest prevalence in South East Asia, with 27% of all cases globally.[3] Repeated episodes of acute rheumatic fever (ARF) with the recurrent autoimmune reaction to Group A streptococcus (GAS) bacterial infection leads to heart valvular damage, caused by the inflammation, and fibrosis cascades.[6] Fibroblast proliferation, cellular adhesion, and extracellular matrix (ECM) accumulation in cardiac fibrogenesis are stimulated and activated by various stimuli such as cytokines, connective tissue growth factors, and activators. Angiotensin II has long been known as the predominant promoter of cardiac fibrosis.[7] Angiotensin II produces its effects through various mechanisms, such as increasing transforming growth factor (TGF-β), induction of mitogen activated protein kinase/ extracellular signal-regulated kinases/ c-Jun N-terminal protein kinase (MAPK/ERK/JNK), Smad2, and also by increasing sST2 as the decoy receptor.[8-10] As a decoy receptor, sST2 binds to IL-33, which should instead bind with its physiological ligand (ST2L), and causes the inhibition of fibrosis inhibition by IL-33.[11] Angiotensin converting enzyme inhibitors (ACEIs) are used in the treatment of cardiovascular diseases including hypertension, cardiac fibrosis, and cardiac hypertrophy.[12] This review elaborated on the role of ACEI in reducing cardiac fibrosis in rheumatic heart disease progression through the inhibition of IL-33/sST2, providing a possible target for therapy against RHD (**Figure 1**).

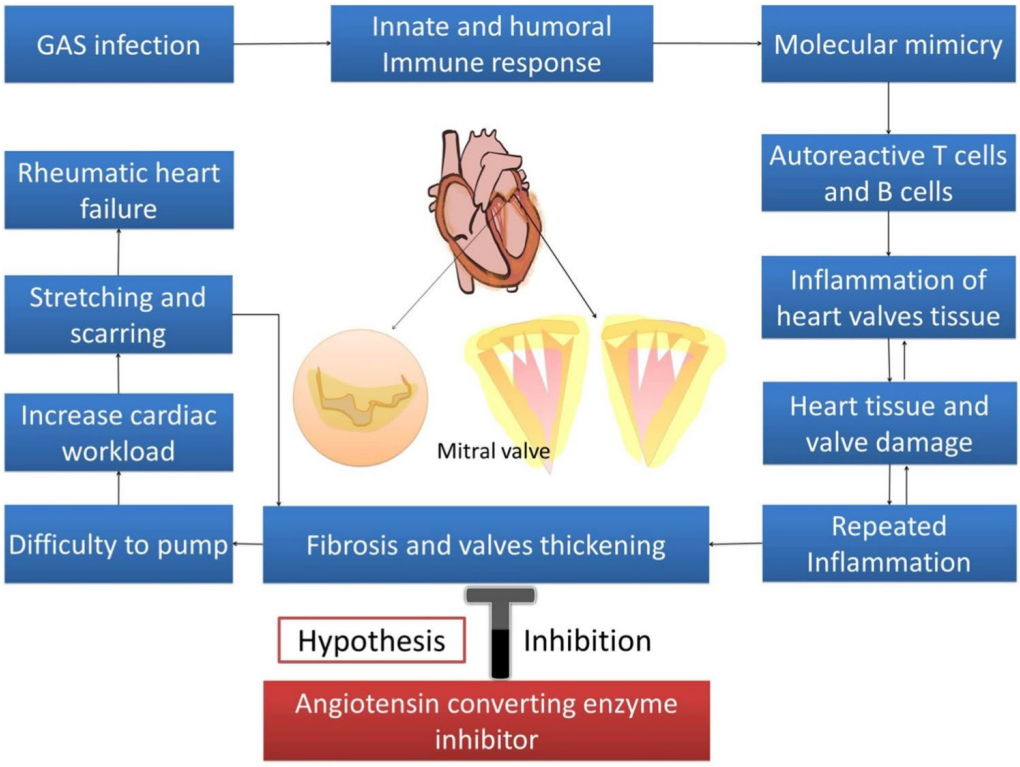


**Figure 1.** Hypothesis

## Immune Response to Gas and Development of RHD

The first response to the GAS infection is the innate immune response. Epithelial cells, neutrophils, macrophages, and DCs are the innate immune response for GAS infection. Epithelial cells work as the physical barrier and also secrete anti-microbial peptides and cytokines to attract immune cell mediators and neutrophil cemotactic factors, and upregulate the expression of TLR (Toll-like receptor).[13,14] Neutrophil chemotactic factors, such as interleukin-8 (IL-8), that are released from the epithelium attracts neutrophils to destroy GAS through the NET (Neutrophil extracellular trap), phagocytosis, and degranulation of the anti-microbial peptide.[15] Repeated infection of GAS will increase IL-17 secretion from Th-17 cells that leads to the recruitment of other neutrophils and macrophages.[16,17] Resident macrophages kill GAS through phagocytosis and through the release of the reactive oxygen species. Macrophages also release cytokines such as IL-6, IL-8, tumor necrosis factor-α (TNF-α), and

Interferon-γ (IFN-γ). IL-6 and IL-8 contribute to the recruitment of neutrophils by promoting the differentiation of naive T-cell to Th-17 cell.[18,19] TNF-α and IFN-γ enhance macrophages and activate monocytes.[20] IFN-γ also regulates IL-1β expression in DCs to prevent hyperinflammation.[21] GAS that invades the epithelium is recognized by DCs via TLR2.[22] This recognition stimulates the release of IL-1β, TNF-α, and IL-12.[23-25] IL-12 induces the polarization of T-cell to Th1.[14,26] IL-6 and TGF-β1 promote the differentiation of CD4+ cell to Th17.[27] Activation of CD4+ cells leads to the propagation of the CD4 effector cells and the differentiation of CD8+ T cells and B cells.[28]

B cells and T cells distinguish GAS antigens and self-antigens through the amino acid sequence and the structural conformation.[29] The antigenic structure of GAS that shares a similarity to a human protein is the M protein. The M protein is identical to the γ-helical coil structure in several valvular proteins, cardiac myosin, and tropomyosin.[6] It causes the T cells to react to the cardiac valves, and autoantibodies formation upregulates Vascular cell adhesion molecule 1 (VCAM1). VCAM1 upregulation worsens the inflammation by causing the adherence of T cells to the endothelium. The autoreactive T cells lead to the granulomatous inflammation that is known as the formation of the Aschoff body.[30] Repeated episodes of ARF as the autoimmune reaction to a GAS bacterial infection leads to permanent heart valvular damage. The heart valve damage is characteristic of RHD, and it could be complicated with heart failure, atrial fibrillation, and stroke, causing significant morbidity, and mortality. Permanent damage to the valves as a consequence of autoimmune reactions occurs in rheumatic disease. This autoimmune reaction is targeted to GAS bacterial infection. Pathogenesis of RHD is influenced by the triad of host, agent, and environment. Infection of GAS occurs in people with susceptible genes.[31] Genome Wide Association Studies found the potential suspicious gene for RHD on chromosome 14q32.33.[32] Molecular mimicry is the mechanism GAS utilizes to cause autoimmunity in RHD. Previous studies found a cross- reactivity of anti-Streptococcal antibodies with N-acetyl-β-D-glucosamine (GlcNAc) and myosin in the serum of patients with rheumatic fever. Myosin is one of main proteins found in reactive group A carbohydrate or streptococcal M protein antigens.[33] Anti-GlcNAc/anti-myosin was reactive to laminin and cytotoxic for human endothelium cells, an ECM protein on the valvular endothelium.[34, 35]

This cytotoxicity results in inflammation and scar tissue caused by T cells. The increase in GlcNac glycation increased the phosphorylation of p38 and ERK1/2, resulting in the increase of stress intolerance.[36] Cross reactivity between GAS antigen and GlcNac generated anti-GlcNac that impairs glycation, thus increasing myocardial stress. Biomechanical and inflammatory myocardial stress induces the release of sST2 from cardiac myocytes.[37, 38] (**Figure 2**).

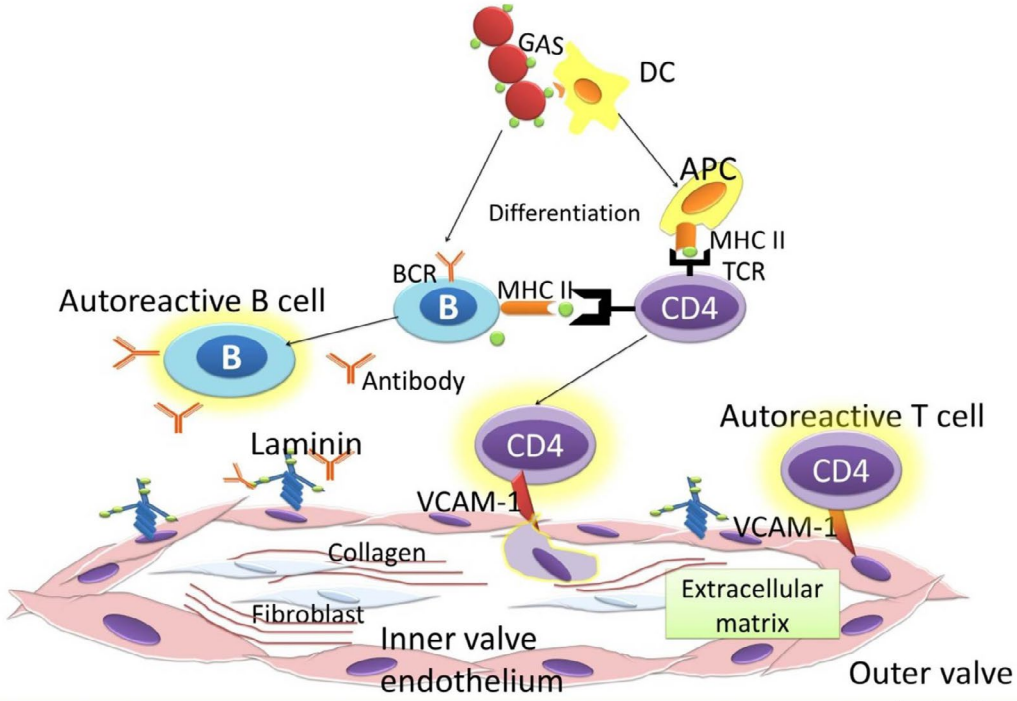


**Figure 2.** Immune response to GAS

## Fibrosis In RHD

Recent advances in understanding the development and pathogenesis of RHD describes the Neo-antigen theory; this theory suggests that GAS organisms could penetrate the subendothelial collagen matrix by utilizing the M protein. The M protein binds to type IV collagen in the CB3 region. It then creates neo-antigens that induce an autoimmune reaction against collagen.[39] Immunological cascades initiated by the antibodies against GAS cause several responses that lead to cardiac fibrosis in RHD. These antibodies recognize and activate the

valvular endothelium to express Vascular Cell Adhesion Molecule-1 (VCAM1). This process results in T cells becoming further activated, and leads to more tissue degradation. This breakdown involves autoantibodies and complement activation, releasing endogenous autoantigens of laminin, collagen, myosin, and tropomyosin. DCs in the valvular endothelium capture these autoantigens, differentiate into antigen presenting cell (APC) in the ectopic Aschoff nodules, and induce autoreactive T cells. These successive cascades contribute to increased inflammation, neovascularization, and tissue fibrosis.[1] In RHD, Angiotensin II induces fibrosis via the stimulation of TGF-β.[40] Interestingly, the administration of Angiotensin II in TGF-β gene-knock-out mice did not cause fibrosis.[41] The binding of TGF-β to its receptor is followed by the phosphorylation of Smad2 protein, a transcriptional protein that acts as a second messenger. Smad2 forms a complex with Smad3 and Smad4. Angiotensin II also enhances the fibrotic effect through stimulating the sST2 decoy receptor, thus will induce more phosporylation of JNK and ERK in the MAPK pathway.[10, 11]

## Crosstalk of MAKP Pathway/TGF-β

MAPK is a protein kinase that converts extracellular stimuli to various cellular responses; it regulates gene expression, metabolism, cell proliferation, growth, differentiation, and survival.[42, 43] MAPK's main downstream pathways comprise of ERK1/2, p38 kinases, and JNKs.[44] MAPK pathways are initiated by one or more growth factors that activate the transmembrane tyrosine kinases. The activated tyrosine kinase activates the signal transductions that regulate the transcription/translation of effector genes.[43] ERK1 and ERK2 could be activated by various growth factors such as epidermal growth factor (EGF), Nerve growth factor (NGF), and platelet- derived growth factor (PDGF).[43, 45] These stimuli bind to the multimolecular receptors, such as receptor tyrosine kinase and G protein-coupled receptor, that transmit signals by activating Ras and convert Guanine diphosphate (GDP) to Guanine triphosphate (GTP). This conversion initiates downstream of effector proteins, including Raf (isoform of the serine/threonine kinase) that activates the signal transducers and activators of transcription that are important regulators of cell growth and proliferation, such as nuclear factor kappa beta (NF-κB), c-Myc, GATA4, c-Jun, and c-Fos.[42, 46–48] JNK phosphorylation is stimulated by stress stimuli such as heat shock, oxidative stress, DNA-

damaging agents, cytokines, and in conditions that lack other growth factors.[49] p38 kinases are also activated by various inflammatory cytokines and oxidative stress through G protein-coupled receptor. IL-1 and TNF-α are known to be able to activate p38 isoforms by increasing the tumor necrosis factor associated factor TNF receptor associated factor (TRAF) adaptor protein.[50]

MAPK pathway also could be activated by TGF-β for promoting cell proliferation, differentiation, and also remodeling of the ECM.[51] The uncontrolled activity of this stimuli could cause pathogenic fibrosis.[52] TGF-β has three known ligands that work through their respective receptors: TGF-βRI, TGF-βRII, and TGF-βRIII.[51] Binding of the ligand to TGF-βRII as the primary receptor in the cell membrane is followed by the phosphorylation and the activation of TGF-βRI (also termed as activin-like kinase 5).[53] The activation of TGF-βRI is continued by the induction of intracellular signaling of Smad2/3 transcription factors via the Smad receptor (R-Smad).[53, 54] Smad2/3 forms heteromeric complexes with Smad4 to regulate profibrotic genes, plasminogen activator inhibitor-1 (PAI-1), integrins, connective tissue growth factors, and metalloproteinases.[53, 55–57] TGF-β can also directly activate ERK, JNK, and p38 MAPK through the induction of their ligands and receptors.[58]

## ST2 Structure and Function

ST2 is a member of the Toll-like receptor superfamily. Based on the extracellular domain, there are three subfamilies of the Toll-like/IL-1 receptor superfamily: the IL-1 receptor like subfamily, the Toll receptor superfamily, and a family comprised of their adaptor proteins. These receptors play a major role in proinflammatory signaling pathways, which are a major contribution in the development of RHD.[59] ST2 is located on chromosome 2q12 as part of the interleukin 1 (IL-1) gene cluster. There are four ST2 isoforms: sST2, ST2L, ST2V, and ST2LV. sST2 (soluble ST2) and the transmembrane (ST2L, also known as IL1RL1-b) promotes the differential mRNA expression .[60] sST2 is similar to ST2L but lacks transmembrane and cytoplasmic domains (such as IL1RL1-b or ST2L and IL1RL1-a or sST2a) and is a truncated soluble receptor that can be found in serum. sST2 is a circulating form, which lacks the transmembrane and cytoplasmic domains and includes nine amino acid C-terminal sequences. The transmembrane form ST2L is constitutively

expressed, primarily in hematopoietic cells (Th2 and mast cells).[61] The structure of ST2L contains three linked immunoglobulin-like motifs, intracellular TLR-1, and the transmembrane segment.

Interleukin-33 (IL-33 or IL-1F11) has been identified as a functional ligand of ST2L.[62] Human IL-33 is mainly expressed and stored in the nucleus of endothelial and epithelial cells. The full length of IL-33 serves as an intranuclear gene regulator, and the mature IL-33 serves as an extracellular cytokine that is released from damaged cells, but it can also be actively secreted by immune cells.[63,64] IL-33 exerts its cellular functions by binding a receptor complex composed of ST2L and IL-1R accessory protein (IL-1RAcP). IL-1RacP is essential for IL-33 signaling through ST2L by enhancing the affinity of IL-33 for ST2L.[59] It binds to ST2L on inflammatory cell membranes. This binding activates MAPK-kinases and activates the inhibitor of the NF-κB kinase (IKK) complex, which makes NF-kB active and able to exert its proinflammatory actions. The binding of sST2 to IL-33 subtracts a molecule from the interaction with ST2L. sST2 interaction with IL-33 could reduce the production and activation of NF-kB, thus it would reduce the inflammatory response. IL-33 has been thought to regulate ST2L and sST2 mRNA transcription.[60]

## ST2 and RHD

IL-33/ST2 signaling initiated by the splitting of caspase-1 leads to the maturation and activation of pro-IL-33 to IL-33. Heterodimer linking of IL-33, ST2, and IL-1RAP leads to dimerization of the TIR domain. This complex activates adaptor protein MyD88, which then activates downstream of IARK-1, IARK- 4, and MAPK kinase through TRAF6 signaling, which in turn activates the activator protein 1 (AP-1) through JNK. TRAF6 also activates the inhibitor of the NF-κB kinase complex, leading to a downstream release of active NF-κB from the complex. It also activates JNK and ERK1/2, following receptor ligation to promote activation of IRF1 which inhibits Foxp3 and GATA3 expressions.[11] A significant upregulation of sST2 was reported in RHD patients.[65] Continuous inflammation promoted by ST2 and mediated by NFκB contributes to the valvular damage in the pathogenesis of RHD. In addition, TRAF 6 also mediates the activation of JNK, resulting in the fibroblast proliferation and collagen deposition in ECM of cardiac valves. This cascade of inflammation and valve fibrosis causes calcification and stiffening of the heart valves in RHD.[66]

## Angiotensin II and TGF-β Signaling

Angiotensin II, through its receptors of AT1 and AT2, elicits its effects on the heart (including heart valves), blood vessels, brain, kidney, fat, and liver.[8] AT2 activation causes the attenuation of TGF-β/MAPK/ERK signaling dependent of Smad.[9] Its pro-fibrotic effects could also be stimulated by the upregulation of TLR2 and TLR4 and the downregulation of TGF-b1 inhibitory pseudo-receptor (BAMBI) by LPS.[67, 68] Angiotensin II also upregulates TGF-β production through non-canonical pathways by activating MAPK/JNK and p38.[8, 69] Ehanire *et al.*[70] proved that angiotensin II stimulates the expression of contractile proteins and fibroblast migration through AT1 receptor, mediated by TGF-βRI (ALK-5). TGF-β increases the synthesis of ECM protein and myofibroblast differentiation by promoting tissue inhibitor metalloproteinase (TIMP), inhibiting matrix metalloproteinase (MMP), and inducing connective tissue growth factor (CTGF) that leads to the fibroblast proliferation, cellular adhesion, and ECM accumulation.[8]

## The Role of ACEIs In Cardiac Fibrosis in RHD

ACEIs are used in the treatment of cardiovascular diseases, or their anti-hypertension and anti-remodeling effects and for their effect on reducing cardiac fibrosis and hypertrophy.[12] ACEIs prevent the hydrolysis of Angiotensin I to Angiotensin II. Angiotensin converting enzyme (ACE) promotes inflammation in the heart, kidney, and vasculature through Angiotensin II as the effector.[12] Renin angiotensin system (RAS) activated by the reduction of renal perfusion results in the release of renin from the juxtaglomerular cells. Renin cleaves liver-produced angiotensinogen to become angiotensin I. Afterward, angiotensin I is converted to angiotensin II by ACE in the lung; at the same time, ACE also degrades bradykinin by the removal of two carboxyl-terminal amino acids.[8, 71, 72] The degradation of bradykinin, which is included in the kallikrein system, could reduce myocardial accumulation and cardio-protection.

Nevertheless, bradykinin negatively regulates the angiotensin II activity in MAPK pathways through the suppression of the Ca2+ response and the Na+ transport.[73] The inhibition of ACE reduces angiotensin II which will cause fibrotic effects through the AT-1 receptor, and also enhance the reduction effect by increasing bradykinin; this would be the advantage of ACEIs over AT-1 receptor blockers on reducing cardiac fibrosis. A study from Abareshi *et al.*[74] showed that ACEIs reduce

inflammation and fibrosis through the reduction of IL-6 and TNF-α. Deijanera *et al.*[75] demonstrated the ACEIs have an effect on reducing TGF- β1, TGF-β2, and Th2 cytokines. ACEIs also induce the apoptosis of cardiac fibroblasts.[76] A clinical trial from Maskito *et al.*[77] showed the reduction of sST2 in heart failure patients. Wei Qiang-Tan *et al.* also demonstrated similar effects of the ACEIs on reducing stimuli and activators of cardiac fibrosis; they showed the ACEIs effect on downregulating Smad and TGF-β activated kinase 1 in mice model.[78]

## ACEIs and IL-33/ST2

Angiotensin II is a peptide produced from angiotensinogen through the enzymatic process of ACE. Angiotensin II is regulated by several enzymes expressed in the heart, by mast cells, and by endothelial and mesenchymal interstitial cells. Angiotensin II stimulates T-cell response and promotes the synthesis of Th1 and Th17 cytokines, specifically IFN-γ and IL-17. ACEIs suppress the release of Th1 and Th17 cytokines and induces regulatory T-cells (Treg) through the NF-κB pathway.[79] Moreover, the contribution of Angiotensin II to inflammatory processes is also marked by its induction to the Monocyte chemoattractant-1 (MCP-1).[80] Angiotensin II enhances the migration, maturation, and the presenting capability of DCs.[81–83] Studies have also demonstrated the role of angiotensin II in cardiac fibrosis. In RHD, angiotensin II induces fibrosis via the stimulation of TGF-β.[40] Angiotensin II also could directly promote sST2, thus promoting IL-33 to bind with sST2 instead of its natural ligand (ST2L).[10] Reciprocally, IL-33/ST2L attenuates the activation of NF-κB downstream by angiotensin II and reduces fibroblast proliferation-induced angiotensin II.[59, 84] ACEIs inhibit the production of Angiotensin II, which then decrease the expression of TGF-β and the reduction of the inflammatory cytokines stimulated by the presence of Angiotensin II. This condition leads to the decreasing of the sST2 as the decoy receptor to "steal" IL-33, thus IL-33 binds to the ST2L and produces cardio-protection against the cardiac fibrosis. The reduction of angiotensin II production and the synergistic effect of bradykinin in ACEIs enhance its cardio-protection effect by directly reducing IL-33 binding to sST2 and through the inhibition of TGF-β/MAPK/Smad signaling in RHD progression (**Figure 3**).

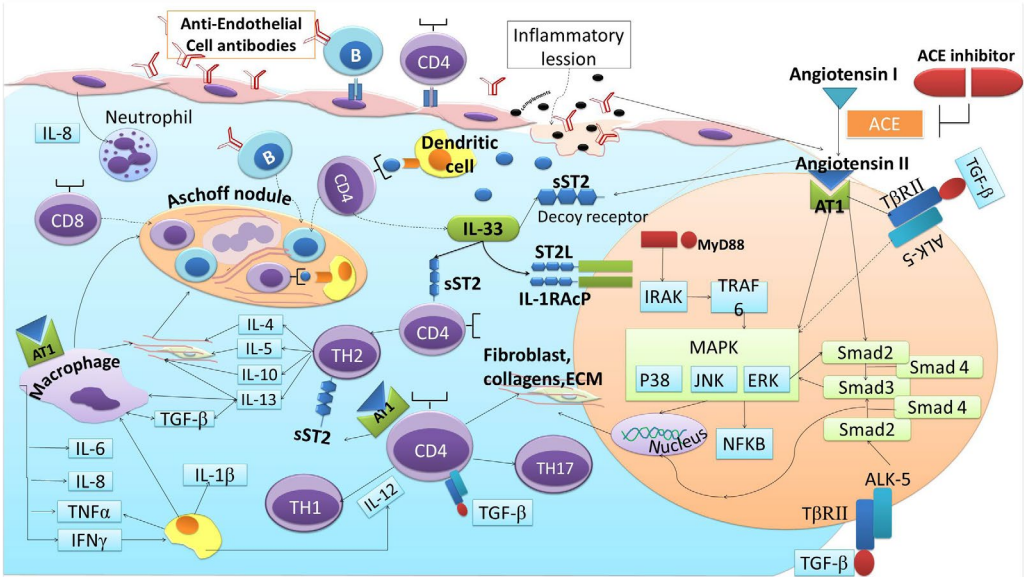


**Figure 3.** ACEI and ST2 involvement in cardiac fibrosis of RHD

## CONCLUSION

GAS autoantibodies induce continuous inflammation and fibrosis through the process of fibroblast proliferation, cellular adhesion, and ECM accumulation in cardiac fibrogenesis that are induced by pro-fibrotic activators and stimuli. Several immunoreactive cells, cytokines, growth factors, and activators are released in response to the activation of autoreactive T cells and B-cells, including the upregulation of TGF-β, Angiotensin II, and sST2. TGF-β induction by Angiotensin II could further increase the binding of IL-33 to sST2 but not ST2L, resulting in the upregulation of Angiotensin II and progression of the fibrotic cycle. This cascade of inflammation and valve fibrosis causes calcification and stiffening of the heart valves in RHD. ACEIs have been widely studied and are proven to reduce the activators and stimuli of cardiac fibrosis that are similar to the activators and stimuli that contribute to the progression of RHD, including sST2. The reduction of angiotensin II production and the synergistic effect of bradykinin in ACEIs enhances its cardio-protection effect by directly reducing IL-33 binding to sST2 and through the inhibition of TGF-β/MAPK/Smad signaling in RHD progression. Therefore, ACEIs may play potential roles in attenuating cardiac fibrosis in RHD via the IL-33/ST2 axis.

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Chapter 3

# Survival analysis of patients with rheumatic MS after PBMV compared with MVS in a low-to-middle-income country.

Ade Meidian Ambari, Budhi Setianto, Anwar Santoso, Bambang Dwiputra, Basuni Radi, Amir Aziz Alkatiri, Arinto Bono Adji, Eliana Susilowati, Fadilla Tulrahmi, Maarten-Jan Cramer, Pieter A. Doevendans

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## ABSTRACT

*Introduction* Rheumatic mitral stenosis continues to be prevalent in developing countries, notably in endemic areas. Over the last few decades, percutaneous balloon mitral valvuloplasty (PBMV) has been established as a lower-cost alternative treatment for mitral stenosis (MS) in low-to-middle-income countries. PBMV has also been suggested to be an effective and safe alternative treatment modality. This study aims to analyse the survival of rheumatic MS patients treated with PBMV compared with those treated with mitral valve surgery (MVS).

*Methods* This study was a national, single-centre, longitudinal study using a survival analysis method in 329 consecutive patients suffering from rheumatic heart disease with severe MS who underwent PBMV compared with 142 consecutive patients with similar characteristics who underwent MVS between January 2011 and December 2016. Survival analysis and event-free duration were determined over a median follow-up of 24 months in the PBMV group and 27 months in the MVS group.

*Results* The results showed that of the 329 consecutive patients in the PBMV group, 61 patients (18.5) had an event (6 patients died and 55 patients were hospitalised), and of the 142 consecutive patients in the MVS group, 19 patients (13.4%) had an event (5 patients died, and 14 patients were hospitalised). The hazard ratio was 0.631 (95% confidence interval, 0.376–1.058; P = 0.081). Longer short-term survival was found in the MVS group but was not statistically significant. Event-free survival was significantly longer in the MVS group (P = 0.002), by 5 months.

*Conclusions* In this study, the efficacy and safety of PBMV was reconfirmed, as PBMV proved to be non-inferior to MVS in survival prognosis, but sustained event-free duration was significantly better in the MVS group than in the PBMV group.

## What's New

- Percutaneous balloon mitral valvuloplasty is non-inferior compared with mitral valve surgery in prognostics for survival, but sustained event-free duration was significantly better in the mitral valve surgery group.
- Higher event-free survival was found in the mitral valve surgery group, but it was not statistically significant
- Event-free duration was significantly 5 months longer in the mitral valve surgery group ($p = 0.002$).

## INTRODUCTION

Rheumatic heart disease (RHD) is a major burden in developing countries and causes most cardiovascular morbidity and mortality in children and young adults. The worldwide prevalence and annual incidence of RHD have been approximated to be >15 million cases and >280,000 cases per year, respectively. Recent studies in Asia have estimated an existing RHD burden of 10.8–15.9 million patients, accounting for 356,000–524,000 deaths per year.[1] RHD is a progressive and chronic condition caused by complement-mediated damage to the atrioventricular valves, frequently including mitral stenosis, that occurs as a result of the inflammatory response in rheumatic fever.[2]

The safety and efficacy of percutaneous balloon mitral valvuloplasty (PBMV) and mitral valve surgery (MVS) have already been established. PBMV is a safe and well-tolerated intervention and is associated with short-term benefits.[3] The increasing burden to reduce health-related expenses makes it compulsory to provide an effective and safe yet economical intervention. Over the last few decades, PBMV has been established as a lower-cost alternative to MVS in low-to-middle-income countries.[4-7] This study was conducted to identify in-hospital survival and short-term survival of rheumatic mitral stenosis patients undergoing PBMV compared with those undergoing MVS.

## METHODS

### *Patient Selection*

We conducted a single-centre, retrospective follow-up study. All 471 consecutive patients admitted with severe mitral stenosis with or without tricuspid valve repair or replacement between January 2011 and December 2016 were included. The study group comprised 329 patients who underwent PBMV and 142 patients who underwent MVS. Patients with congenital heart disease or those who received non-mitral valve surgery or coronary artery bypass grafting were excluded from this study. The data were acquired from medical records and local databases.

### *Treatment Strategy*

The definite treatment strategy for patients with severe MS, either PBMV or MVS, was determined during the pre-surgery conference attended by cardiologists and surgeons and was based on echocardiographic data, patient age, and comorbidities. Our institutional review board approved the retrospective analysis of the clinical data of these subjects.

Treatment indications followed the ESC guidelines for intervention in MS. PBMV was indicated in symptomatic patients with a valve area <1.5 $cm^2$ if symptoms could not be explained by another cause, and if the anatomy was favourable, in symptomatic patients with a contraindication or a high risk for surgery, as well as in asymptomatic patients without unfavourable clinical or anatomical characteristics for PBMV with high thromboembolic risk and/or a high risk of haemodynamic decompensation. PBMV was contraindicated if the mitral valve area >1.5 $cm^2$, if there was a presence of left atrial thrombus, if a patient had more than mild mitral regurgitation, in the case of severe or bicommissural calcification, in the case of an absence of the commissural fusion, in patients with severe concomitant aortic valve disease or severe combined tricuspid stenosis, if a patient had regurgitation that required surgery, and in patients with concomitant coronary artery disease that required bypass surgery. Mitral valve surgery is indicated in symptomatic patients who are not suitable for PBMV.[8] The Wilkins score was calculated. A mitral valve

with a score less than 8 indicated that the patient was a candidate for PBMV. In patients with a score ≥8, especially in those with more than moderate mitral regurgitation, surgical therapy was performed, except in patients with serious comorbidities.[9]

### *Treatment Technique*

Percutaneous balloon mitral valvuloplasty procedures were performed by a percutaneous trans-septal anterograde approach and the Inoue balloon technique, according to the stepwise technique procedure, under echocardiographic guidance. The mitral valve area was calculated using the Gorlin formula.[10] MVS was performed with mitral valve replacement or mitral valve repair. Mitral valve replacement was conducted in 115 of 142 patients (81%), and mitral valve repair was conducted in 27 of 142 patients (19%).

### *Measurement*

The diagnosis of rheumatic mitral valve disease was made by echocardiography. Echocardiography was performed and analysed in the same centre. Rheumatic valve diseases were diagnosed using the World Heart Federation Criteria for Rheumatic Heart Disease. Comprehensive 2-dimensional and colour Doppler echocardiographic evaluation was performed in all patients before PBMV or MVS. In addition to routine measurements of cardiac chamber dimensions and ejection fraction by the modified Simpson method, the mitral gradient and the peak pressure gradient of tricuspid regurgitation were calculated. The morphological features of the mitral valve were categorised as previously described, and the total echocardiographic score was obtained by adding the scores of each of the following individual morphological features: leaflet mobility, thickness, calcification, and subvalvular lesions. The mitral valve area was measured by direct planimetry to calculate the mitral gradient and the peak pressure gradient of tricuspid regurgitation.

### *Follow-up*

Follow-up data were collected from January until June 2017. The data were obtained either from medical records during patient visits to the outpatient clinic or during hospitalisation or by telephone interviews. The endpoints were defined as the clinical events of cardiovascular death and hospitalisation.

### *Data Analysis*

Categorical variables are presented as numbers and percentages and were compared by $\chi^2$ or Fisher's exact test. Continuous variables and actuarial survival rates are expressed as the mean standard deviation and were compared by unpaired *t*-tests, except for follow-up duration, which is expressed as a median. The Cox proportional hazards model was used to determine whether the event-free survival differed significantly between PBMV and MVS patients after controlling for the differences in their pre-procedural risk profiles. Bivariate analysis was performed with a Cox model to determine the risk factors of an outcome. Variables were entered in a Cox multivariate model with a backward selection procedure and a significance level of $P < 0.05$ to prevent failure in identifying variables known to be important.[11] Two-way interactions were studied between these selected variables with a stratified log-rank test. The final Cox multivariate model was established by a backward selection of these variables with a significance level of $P < 0.05$. Cumulative survival curves were determined according to the Kaplan-Meier method (Fig. 1). The analysis was performed with SPSS.

## RESULTS

### *Baseline Characteristics and short-term Outcomes*

This study involved a total of 471 patients, comprising 329 PBMV patients and 142 MVS patients. From 142 patients who underwent MVS, mitral valve repair was performed in 26 patients (18.3%) with mitral valve replacement in 116 patients (81.7%). The median follow-up was 24 months in the PBMV group and 27 months in the MVS group. The endpoints of the present study were the frequency of objective clinical events, including cardiovascular death and hospitalisation. The baseline characteristics of all patients are summarised in Tab.1.

The youngest age of PBMV patients was 11 years, and the eldest was 72 years. In MVS patients, the mean age distribution of patients was 41.2 years (39.36–43.12), with a median age of 40 years and a standard deviation ±11.3. The youngest MVS patient was 16 years old, and the eldest was 67 years. In PBMV patients, we found mostly women with atrial fibrillation and normal BMI. More than 50% of patients used anticoagulant and diuretic medications. From 329 BMV patients, we found that 61 (18.5%) patients had an event (6 patients died and 55 patients were hospitalised). From 142 surgery patients, 19 (13.4%) had an event (5 patients died and 14 patients were hospitalised). The frequency distribution of events is summarised in Tab.2.

Bivariate analysis showed some predictors that could influence the study outcome. In PBMV and MVS patients, there was no association between these predictors and the observed events. The results of the bivariate analysis are summarised in Tab.3. In the univariate Cox regression analysis, no variable affected patient survival following the PBMV or MVS procedure. Multivariate Cox regression was performed, showing that 3 variables became confounding factors in this study (Tab.4). MVS patients were less likely to have events after adjusting for these variables (adjusted hazard ratio [HR] = 0.6).

**Table 1.** Frequency distribution of patient characteristics in the PBMV and MVS groups

| Variable | PBMV (n = 329) | MVS (n = 142) |
|---|---|---|
| Age, y | 39.3 ± 1.6 | 41.2 ± 11.3 |
| Male, n (%) | 87 (26.4%) | 57 (4.1%) |
| Smokers, n (%) | 35 (10.6%) | 28 (19.7%) |
| Diabetes Mellitus, n (%) | 6 (1.8%) | 9 (6.3%) |
| Hypertension, n (%) | 29 (8.8%) | 13 (9.2%) |
| Dyslipidaemia, n (%) | 3 (0.9%) | 10 (7%) |
| Anticoagulant, n (%) | 226 (68.7%) | 142 (100%) |
| ACE Inhibitor, n (%) | 1 (0.3%) | 86 (60.6%) |
| Beta Blocker, n (%) | 149 (45.3%) | 68 (47.9%) |
| Digitalis, n (%) | 146 (44.4%) | 35 (24.6%) |
| Diuretic, n (%) | 291 (88.4%) | 87 (61.3%) |
| AF, n (%) | 200 (60.8%) | 83 (58.5%) |
| BMI, n (%): | | |
| Underweight | 68 (20.7%) | 46 (33.3%) |
| Normal | 136 (41.3%) | 58 (42%) |
| Overweight | 57 (17.3%) | 12 (8.7%) |
| Obesity | 68 (20.7%) | 22 (15.9%) |
| Wilkins Score | Median score= 7 | Median score= 8 |

*PBMV* percutaneous ballon mitral valvuloplasty, *MVS* mitral valve surgery, *ACE* angiotensin-converting enzyme, *AF a*trial fibrilation, *BMI* body mass index

**Table 2.** Frequency distribution of events in the PBMV and MVS groups

| Variable | PBMV (n= 329) | MVS (n=142) |
|---|---|---|
| Event (Mortality/Morbidity), n (%) | 61 (18.5%) | 19 (13.4%) |
| Mortality, n | 6 | 5 |
| Rehospitalization, n | 55 | 14 |
| Congestive Heart Failure, n | 49 | 13 |
| Repeat Intervention, n | 2 | 0 |
| Arrhythmia | 3 | 0 |
| Cerebrovascular Accident, n | 1 | 1 |

*PBMV* percutaneous ballon mitral valvuloplasty, *MVS* mitral valve surgery

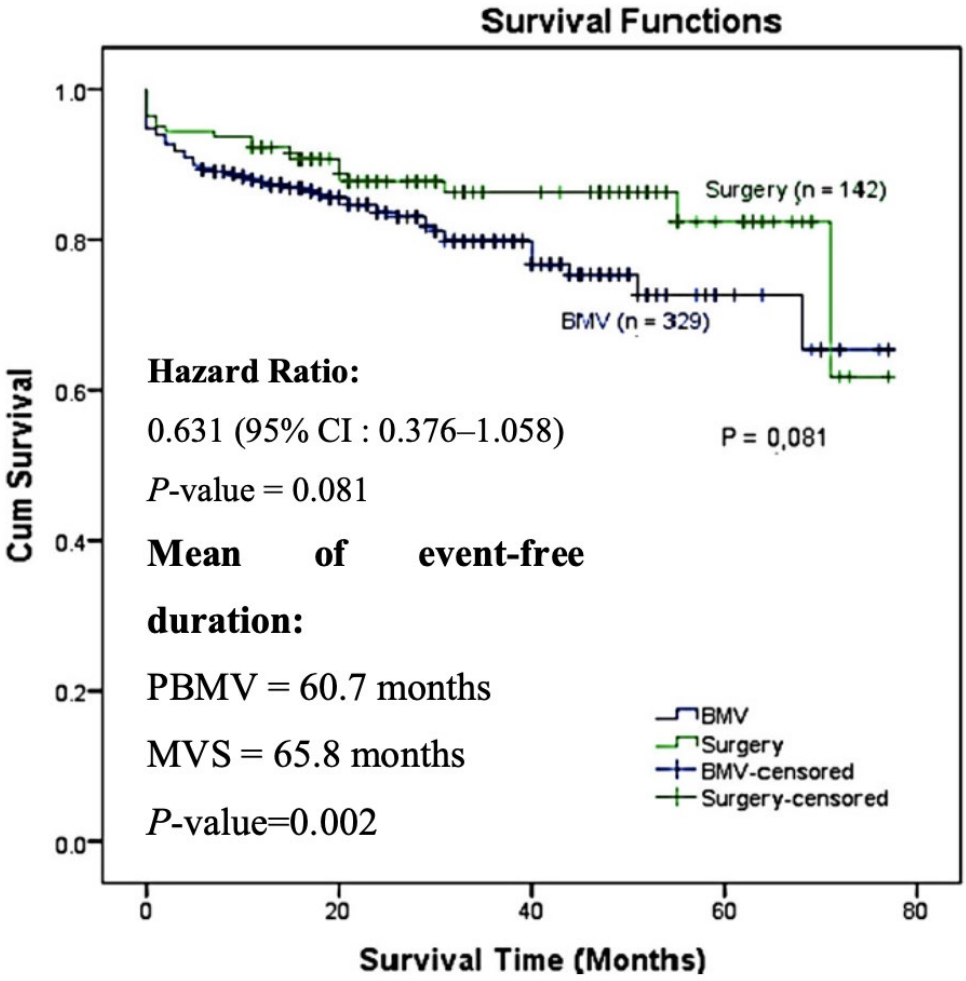


**Figure 1.** Cox regression & Kaplan-Meier curve analysis (CI confidence interval, ***PBMV*** percutaneous balloon mitral valvuloplasty, ***MVS*** mitral valve surgery, ***BMV*** balloon mitral valvuloplasty)

**Table 3.** Bivariate analysis predictors of event outcomes

| Variable | PBMV (n = 329) | | | MVS (n = 142) | | |
|---|---|---|---|---|---|---|
| | n | HR (95% CI) | P value | n | HR (95% CI) | P value |
| Male | 16 (18.4%) | 1.0 (0.6–1.8) | 0.977 | 8 (14%) | 1.1 (0.4–2.7) | 0.894 |
| Age | Mean 39.3 ± 1.6 | 1.0 (0.9-1.0) | 0.593 | Mean 41.2 ± 11.3 | 1.0 (0.9-1.1) | 0.194 |
| Wilkins Score | Median 7 | 1.1 (0.9-1.4) | 0.485 | Median 8 | 1.2 (0.7-1.1) | 0.555 |
| Smokers | 6 (17.1%) | 0.9 (0.4–2.3) | 0.957 | 4 (14.3%) | 1.0 (0.3–3.1) | 0.979 |
| DM | 1 (16.7%) | 0.8 (0.1–5.7) | 0.812 | 0 | - | 0.456 |
| Hypertension | 8 (27.6%) | 1.6 (0.8–3.4) | 0.222 | 2 (15.4%) | 1.3 (0.3–5.9) | 0.692 |
| Dyslipidaemia | 1 (33.3%) | 3.1 (0.4–22.4) | 0.625 | 0 | - | 0.434 |
| Anticoagulant | 45 (19.9%) | 1.3 (0.7–2.3) | 0.404 | 19 (13.4%) | - | - |
| ACE Inhibitor | 1 (100%) | 9.3 (1.3-67.7) | 0.028 | 11 (12.8%) | 0.9 (0.4–2.5) | 0.954 |
| Beta blocker | 26 (17.4%) | 0.9 (0.6–1.5) | 0.743 | 10 (14.7%) | 1.1 (0.5–2.8) | 0.807 |
| Digitalis | 27 (18.5%) | 0.9 (0.5–1.4) | 0.588 | 3 (8.6%) | 0.5 (0.1–1.7) | 0.254 |
| Diuretic | 56 (19.2%) | 1.6 (0.6–4.0) | 0.313 | 10 (11.5%) | 0.6 (0.2–1.4) | 0.239 |
| ECG (AF) | 42 (21%) | 1.5 (0.8–2.5) | 0.173 | 10 (12%) | 0.8 (0.3–1.9) | 0.604 |
| BMI: | | | | | | |
| Underweight | 13 (19.1%) | 1.0 | | 5 (10.9%) | 1.0 | |
| Normal | 24 (17.6%) | 0.9 (0.5–1.9) | 0.944 | 6 (10.3%) | 1.0 (0.3–3.3) | 0.995 |
| Overweight | 9 (15.8%) | 0.8 (0.3–1.9) | 0.643 | 1 (8.3%) | 0.8 (0.1–6.9) | 0.845 |
| Obesity | 15 (22.1%) | 1.1 (0.5–2.3) | 0.791 | 6 (27.3%) | 3.3 (0.9–10.9) | 0.055 |

*PBMV* percutaneous ballon mitral valvuloplasty, *MVS* mitral valve surgery, *HR* hazard ratio, *CI* confidence interval, *ACE* angiotensin-converting enzyme, *AF* atrial fibrilation, *BMI* body mass index

**Table 4.** Multivate analysis predictors of event outcomes

| Variable | HR | 95% CI | P value |
|---|---|---|---|
| Treatment | 0.6 | 0.3–1.1 | 0.081 |
| Wilkins Score | 1.1 | 0.9–1.4 | 0.303 |
| Digitalis | 0.7 | 0.4–1.1 | 1.124 |
| Diuretic Use | 1.2 | 0.6–2.4 | 0.648 |

*HR* hazard ratio, *CI* confidence interval

## DISCUSSION

The main finding of this study is that there were no significant differences in survival prognosis between groups. Short-term survival was similar in both groups, and the hazard ratio for the clinical events after MVS compared with PBMV was 0.631 (95% confidence interval [CI], 0.376–1.058; *P* = 0.081). Sustained life expectancy was found in the MVS group compared with the PBMV group. The event-free duration was significantly longer in the MVS group (*P* = 0.002), by 5 months.

The patient characteristics that were assessed in this study were sex, age, body mass index (BMI), smoking status, diabetes mellitus (DM), hypertension, dyslipidaemia, anticoagulant (warfarin) use, angiotensin-converting enzyme inhibitor use, beta blocker use, digitalis use, diuretic use and the presence of atrial fibrillation. These variables did not interfere with the survival results, because the bivariate analysis showed that none of them was significantly correlated with the outcome events. This result was in accordance with that of Song *et al.* (2010), who identified the long-term outcomes between PBMV and MVS in a total of 561 consecutive patients between January 1995 and December 2000, with a median follow-up of 109 months. The previous study showed that 20 patients (13%) who underwent MVS died, and 78 patients (19%) who underwent PBMV died. Based on the unadjusted survival results, both groups had the same event-free survival rate (HR = 1.51; 95% CI: 0.914–2.496; *P* = 0.1079). After the data were adjusted for age, left atrial anteroposterior diameter, and echo findings, the hazard ratio became 3.729 (95% CI: 1.962–7.082; *P*-value <0.001). The results led to the conclusion that patients who receive MVS have better longer-term survival rates than those who receive PBMV.[12]

The results of research conducted by Chen *et al.* (2015) indicated that PBMV is a safe and effective procedure for RHD patients with MS and tricuspid regurgitation. This procedure can relieve symptoms, reduce the magnitude of tricuspid regurgitation and can improve the quality of life and patient prognosis, but the long-term effects need to be monitored. In this study, the tricuspid regurgitation area (TRA) increased when the mitral valve area (MVA) decreased, and there was a reverse relationship between the two ($r = -0.8$, $t$ =

27.115, $P < 0.01$). In particular, tricuspid regurgitation contributes to increased morbidity and mortality despite surgical and percutaneous measures of mitral valve disease.[13] Kim *et al.* (2007) compared long-term outcomes after mitral valve replacement or repeated PBMV in patients with restenosis after a previous balloon valvotomy. In a survival analysis until 40 months postoperatively, both procedures had the same event-free survival, but 6 years and 9 years of follow-up showed that mitral valve replacement had significantly longer event-free survival than repeated PBMV.[10] Additionally, a study by Lee *et al.* (2015) aimed to determine the outcomes of mitral valve repair in patients with mitral stenosis after PBMV.[14] The results showed that the mean valve area using planimetry increased (1.16–1.62; $P = 0.0001$), the pressure half time using Doppler ultrasound decreased (202.4–152; $P = 0.0001$), and the mean pressure gradient using Doppler ultrasound decreased (9.4–5.8; $P = 0.0021$).

Based on these results, mitral valve repair can be suggested as an alternative method for patients with mitral restenosis who have received PBMV.[14-19] Song *et al.* (2010) found that patients with abnormal echocardiography findings and high atrial fibrillation rhythm showed better outcomes after MVS. This statement was confirmed by other studies,[20-25] showing that MVS has advantages over PBMV because, in cases of the combination of MS with tricuspid regurgitation and atrial fibrillation rhythm, MVS is the best choice for treatment, but our study calculated atrial fibrillation rhythm as a possible confounding factor and found that it was not statistically significant to this research.

## *Limitations*

This study was a single-centre study using an observational study design with inherent limitations. Different follow-up times were unavoidable, but the median time follow-up in this study showed no significant differences between the groups. This study is too limited by the short follow-up period to determine survival in the PBMV and MVS groups. A longer time to follow-up and a larger sample size may have led to more reliable results.

## CONCLUSIONS

In this retrospective, observational single-centre study, the short-term safety and efficacy of PBMV was reconfirmed, as PBMV proved to be non-inferior to MVS in survival prognosis, but the sustained survival duration was significantly better in the MVS group.

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Chapter 4

# Improvement of exercise capacity after early phase II cardiac rehabilitation in patients who undergo rheumatic mitral valve surgery.

Ade Meidian Ambari, Budhi Setianto, Anwar Santoso, Basuni Radi, Bambang Dwiputra, Eliana Susilowati, Fadilla Tulrahmi, Pieter A. Doevendans, Maarten-Jan Cramer

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## ABSTRACT

***Background*:** Rheumatic heart disease still become a major concern in developing countries. Recent studies showed the benefits of early phase II cardiac rehabilitation (CR) on improving the exercise capacity but the evidence in patients after rheumatic mitral valve surgery due to rheumatic heart disease is limited. This study aims to investigate the effects of early phase II CR program on increasing exercise capacity in the rheumatic mitral valve surgery patients.

***Methods*:** This is a cohort retrospective study. A review of medical records identified 254 patients who underwent early phase II CR after rheumatic mitral valve surgery between July 2009 – June 2019. Effects of CR was assessed by 6 Minutes Walking Distance (6MWD) pre and post early phase II CR and peak oxygen uptake ($VO_2$ peak) calculated by Cahallin formula. In this study, we observed and analyzed the increasing of 6MWD and $VO_2$ peak.

***Results*:** Our findings showed that 6MWD and $VO_2$ peak increased significantly in these patients after early phase II CR program ($p = 0.001$). Mean of 6MWD increased from 316.3 ± 71.7 meters to 378.6 ± 60.3 meters and $VO_2$ peak increased from 7.7 ±2.4 mL/kg/min to 8.9 ± 2.2 mL/kg/min. The mean difference of 6MWD was 62.3 meters and $VO_2$ peak was 1.2 mL/kg/min. There was a strong correlation between $VO_2$ peak and 6MWD ($r = 71\%$; $R^2 = 51\%$; $p = 0.001$).

***Conclusion*:** Early phase II CR in patients with Rheumatic Mitral Stenosis after mitral valve surgery improved the exercise capacity. Based on 6MWD, we can predict the value of $VO_2$ peak patients with rheumatic mitral stenosis surgery patients.

## INTRODUCTION

Rheumatic Heart Disease (RHD) is a major burden disease, especially in developing countries. Based on total cases summarized by WHO, it was found about 79% cases in developed countries.[1] Rheumatic mitral stenosis had a significant impact on morbidity and mortality. In many countries such as Asia, the incidence rate of rheumatic fever is about more than 10 cases per year.[1]

Cardiac rehabilitation as has been known to improve cardiopulmonary function, endurance capacity in patients with cardiovascular disease as well as post heart surgery patients. Beside its benefits of reducing blood lipid level, blood pressure, body weight, smoking habit, its cardiac rehabilitation has multiple other potentially beneficial effects including improving endothelial function and myocardial flow reserve.[2-7] Cardiac rehabilitation also could improve exercise capacity and reduce morbidity in post-heart valve surgery patients.[8] Cardiac rehabilitasion (CR) consists of 3 phases: the phase I is in-hospital rehabilitation. In this phase, the patient would be given low-intensity exercise, education, risk control, and encouragement to step up in phase II CR. Phase II is outpatient rehabilitation and supervised by the cardiac rehabilitation team. Phase II is aimed to increase the strength and patients get stronger and active after leaving the hospital. Phase III is long term rehabilitation of phase II CR (home-based). In this phase, the cardiac rehabilitation team will give a prescription for specific exercise based on METS result in phase II and improve their quality of life.[9,10]

There are 2 ways to assessing exercise capacity status in patient with heart disease. First, the 6-minute walk test (6MWT) is one of the field walking test that usually used to examine patient because easy to administer and inexpensive. This test aims to see functional capacity by instruct patient to walk quickly over 6 minutes to get maximal distance.[11] Maximal distance reflects patients physical ability. Second, $VO_2$ is a gold standard parameter for aerobic capacity that measured by Cardiopulmonary Exercise Testing (CPET) beside 6MWT. CPET is an expensive method that needs equipment, professional trainer, and not all hospital provides this test to examine their patient.[12]

This study investigated the increase of exercise capacity before and after phase II cardiac rehabilitation, measured with 6 Minute Walking Test (6MWT) in patients with rheumatic mitral valve stenosis in Department of Cardiology and Vascular Medicine, University of Indonesia, National Cardiac Center Harapan Kita Hospital Jakarta, Indonesia.

## METHODS

### *Study Design and Data Source*

We conducted an observational cohort retrospective study to evaluate the current use of early phase II CR among post MVR patients. We obtained data regarding CR use among post-Mitral Valve Surgery patients in the National Cardiovascular Center Harapan Kita Hospital Jakarta Indonesia from July 2009 – June 2019. The institutional review board of National Cardiovascular Center Harapan Kita Hospital, Faculty of Medicine, University of Indonesia granted the study.

### *Study Setting and Participants*

The study population included patients from early phase II CR in the National Cardiovascular Center Harapan Kita Hospital Jakarta, Indonesia. Patients who came to preventive and rehabilitative installation for phase II CR following the MV surgery who were previously MS due to RHD were included in this study. RHD MS patients with other valve abnormality were also excluded in this study. RHD patients without MS were excluded from this study.

### *Measurements*

Rheumatic valve diseases were diagnosed using the World Heart Federation criteria for RHD.[13] A comprehensive 2-dimensional color Doppler echocardiographic evaluation was performed, and mitral stenosis patients in the subcategory B of definite RHD category, which is defined as mitral stenosis with a mean gradient of ≥4 mmHg and at least two morphological changes of RHD of the MV. Typically, leaflets are thickened and the posterior leaflet is

relatively immobile and moves parallel during diastole with the anterior MV leaflet. Our institutional review board approved the retrospective analysis of the subjects' clinical data. After surgery, all patients underwent phase II CR. CR aims to improve physical, psychological, and general functioning during the recovery period after cardiovascular events. It comprises an integrated multidisciplinary approach involving physical exercise, lifestyle modification, control of risk factors, and psychological intervention.

In the present study, phase II CR was performed in a specialized CR center of the Harapan Kita National Cardiovascular Center in Jakarta, Indonesia. Phase II CR was performed 2 weeks after mitral valve surgery in patients with RHD. The Phase II CR program consisted of a minimum of 12 sessions. The II CR program consisted of aerobic and resistance exercises. The aerobic exercise comprised 30 minutes on a treadmill, ergo-cycle, or arm-cycle. Resistance exercise is not always performed, but individualized in some patients, and did not begin until 2-3 weeks after the aerobic exercise was adapted. Resistance training is contraindicated in patients with: unstable angina, uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg), uncontrolled dysrhythmias, a recent history of congestive heart failure that has not been evaluated and effectively treated, severe stenotic or regurgitant valvular diasease, and hypertrophic cardiomyopathy. The recommended beginning resistance exercise is with 1- to 2-lb dumbbells or wrist weights. The program consists of 8 to 10 exercises, 2 to 3 days per week, with 1 set of 10 to 15 repetitions to moderate fatigue (RPE 12 to 13, somewhat hard). Patients will progress by 1- to 2-lb increments every 1 to 3 weeks depending on signs or symptoms and adaptation to training.[7,14]

To carry out the 6MWT before and after the phase II CR program, we referred to the American Thoracic Society's guideline.[8] The test was performed indoors. The patient was instructed to wear comfortable clothing and shoes for walking and to avoid vigorous exercise for 2 hours before the test. Warm-up exercises were not performed before the test. The patient was then instructed to sit on a chair adjacent to the start point of the 6MWT for 10 minutes before the start. During this time, the patient's pulse and blood pressure were measured. Baseline dyspnea and overall fatigue were measured using the Borg scale in the standing position. The timer was set to 6 minutes and the lap counter to

zero. Patients were instructed to walk as far as they could in the hallway for 6 minutes. Slowing down, stopping, and resting were permitted if necessary. Leaning against the wall was also permitted while resting. Patients were shown how to carry out the 6MWT before they started the test, and they started when they felt ready.[16] $VO_2$ peak in this study was calculated using Cahallin formula[9] as follows:

$VO_2$ peak= (6MWD x 0.06) – (0.104 x age) + (0.052 x weight) + 2.9

### *Statistical Analysis*

Bivariate analysis between pre and post phase II CR were analyzed using paired t-test to see mean difference of 6MWD and $VO_2$ peak. Correlation and linear regression analysis were analyzed to determine the correlation value obtained from both variables and see predicted values of the dependent variable on the independent variable. Significance level of this study was $p \leq 0.05$. All statistical analysis performed with SPSS software.

## RESULTS

A total of 254 patients was followed-up in this study, with the baseline characteristics that was summarized in Table 1. As much as 87% of the study participants performed 12 sessions of the phase II CR, while the other 13% patients failed to achieve a minimum of 12 sessions of phase II CR. But there was no significant difference of the outcomes from individuals who completed 12 sessions compared to the individuals who did not achieve the minimum of 12 sessions phase II CR. The average of phase II CR duration in our study was 42.38 days.

Both 6MWD and $VO_2$ peak of the patients were significantly increased after the phase II CR ($p = 0.001$), with the 6MWD improvement from 316.3±71.7 meters to 378.6±60.3 meters and the $VO_2$ peak improvement from 7.7±2.4 ml/kg/min to 8.9±2.2 ml/kg/min.

In this result on Table 2, we found that strong and positive relationship between 6MWD post and $VO_2$ peak post ($r = 0.715$, $p = 0.001$). Based on coefficients B, it can be interpreted that $VO_2$ peak post will increase by 2.7 mL/kg/min if 6MWD post increases every 100 meters.

**Table 1.** Baseline characteristics of subjects

| Variables | Total (n = 254) |
|---|---|
| **Demographics** | |
| Sex, n (%) | |
| Female | 159 (62.6) |
| Male | 95 (37.4) |
| Age, y | 41.6 ± 10.3 |
| BMI, kg/m2 | 28.5 ± 64.2 |
| SBP, mmHg | 105.7 ± 54.7 |
| DBP, mmHg | 62.4 ± 10.7 |
| HR, bpm | 83.7 ± 15.7 |
| **Risk Factors** | |
| Smoker, n (%) | 48 (18.9) |
| Diabetes, n (%) | 17 (6.7) |
| Hypertension, n (%) | 19 (7.5) |
| Dyslipidemia, n (%) | 12 (4.7) |
| CAD History, n (%) | 7 (2.8) |
| CVA History, n (%) | 3 (1.2) |
| Aortic Regurgitation, n (%) | 69 (40.8) |
| Mitral Regurgitation, n (%) | 64 (38.1) |
| Tricuspid Regurgitation, n (%) | 134 (79.3) |
| Pulmonic Regurgitation, n (%) | 48 (28.7) |
| **Medications** | |
| ACEI, n (%) | 225 (88.6) |
| Bblocker, n (%) | 198 (78.0) |
| Statin, n (%) | 12 (4.7) |
| **Surgery** | |
| Left Atrium Surgery, n (%) | 46 (18.1) |
| Surgery Type, n (%) | |
| MVr | 6 (2.4) |
| MVR | 248 (97.6) |
| **Echocardiographic Examination** | |
| Ejection Fraction, % | 56.4 ± 11.4 |
| Left Atrium Size, mm | 50.3 ± 9.9 |
| LVIDd, mm | 47.8 ± 8.3 |
| LVIDs, mm | 33.0 ± 7.3 |
| TAPSE, mm | 14.0 ± 6.1 |

CAD coronary artery diasease, CVA cerebrovascular attack, ACEI Angiotensin converting enzyme inhibitor, MVr mitral vale repair, MVR mitral valve replacement, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate

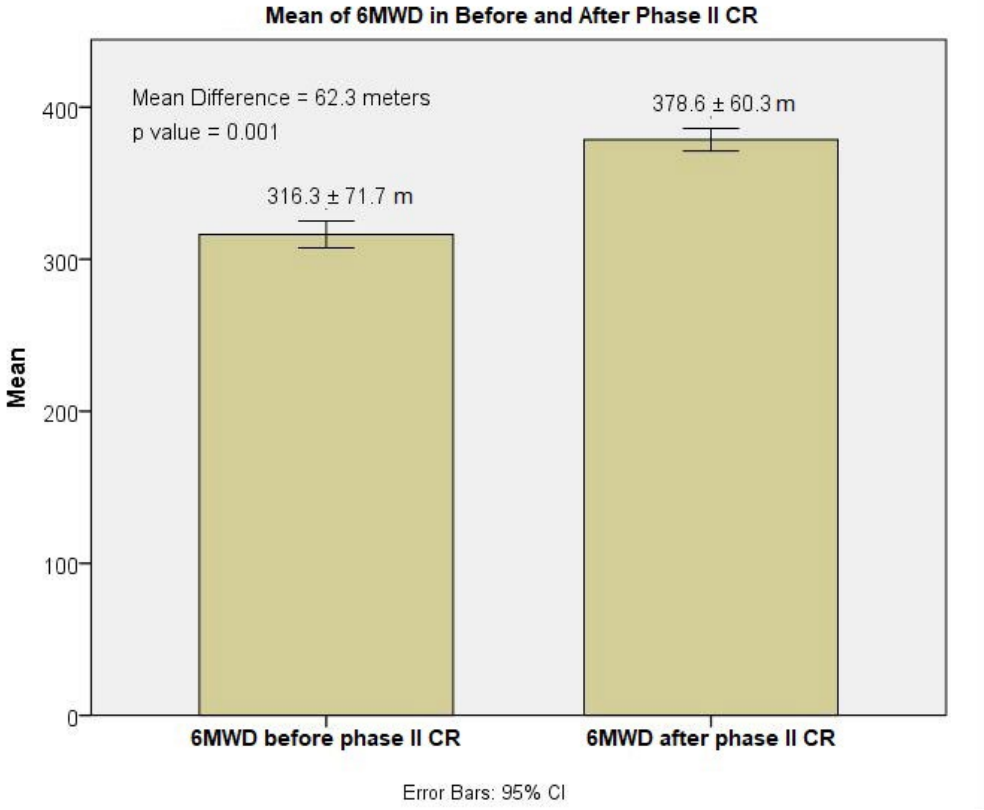



**Figure 1.** Mean of 6MWD in before and after phase II CR

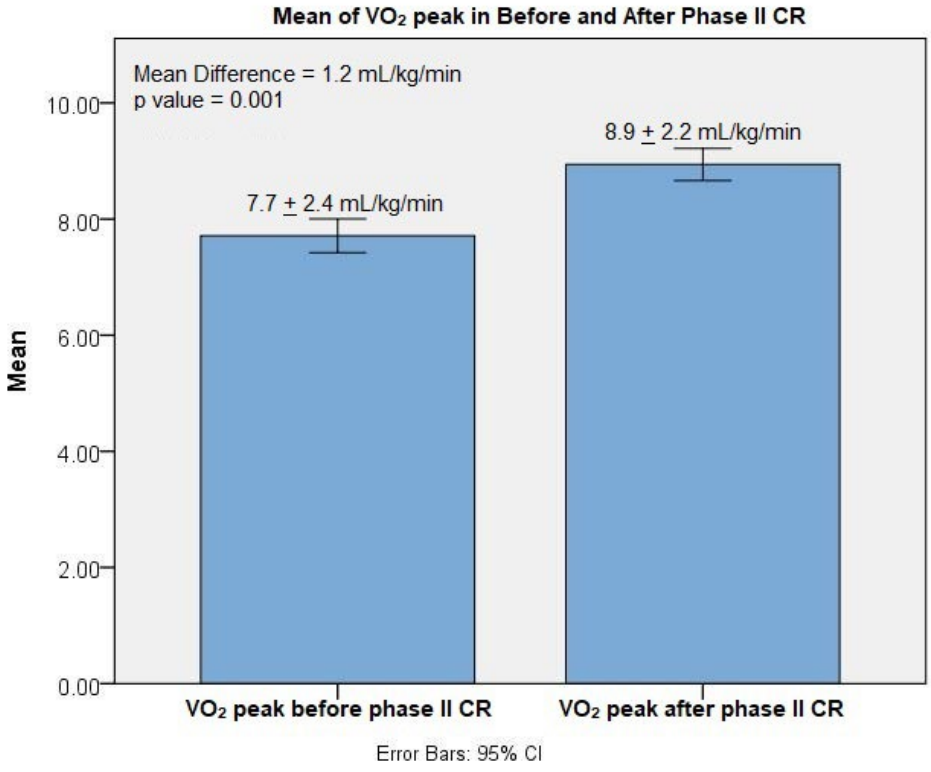
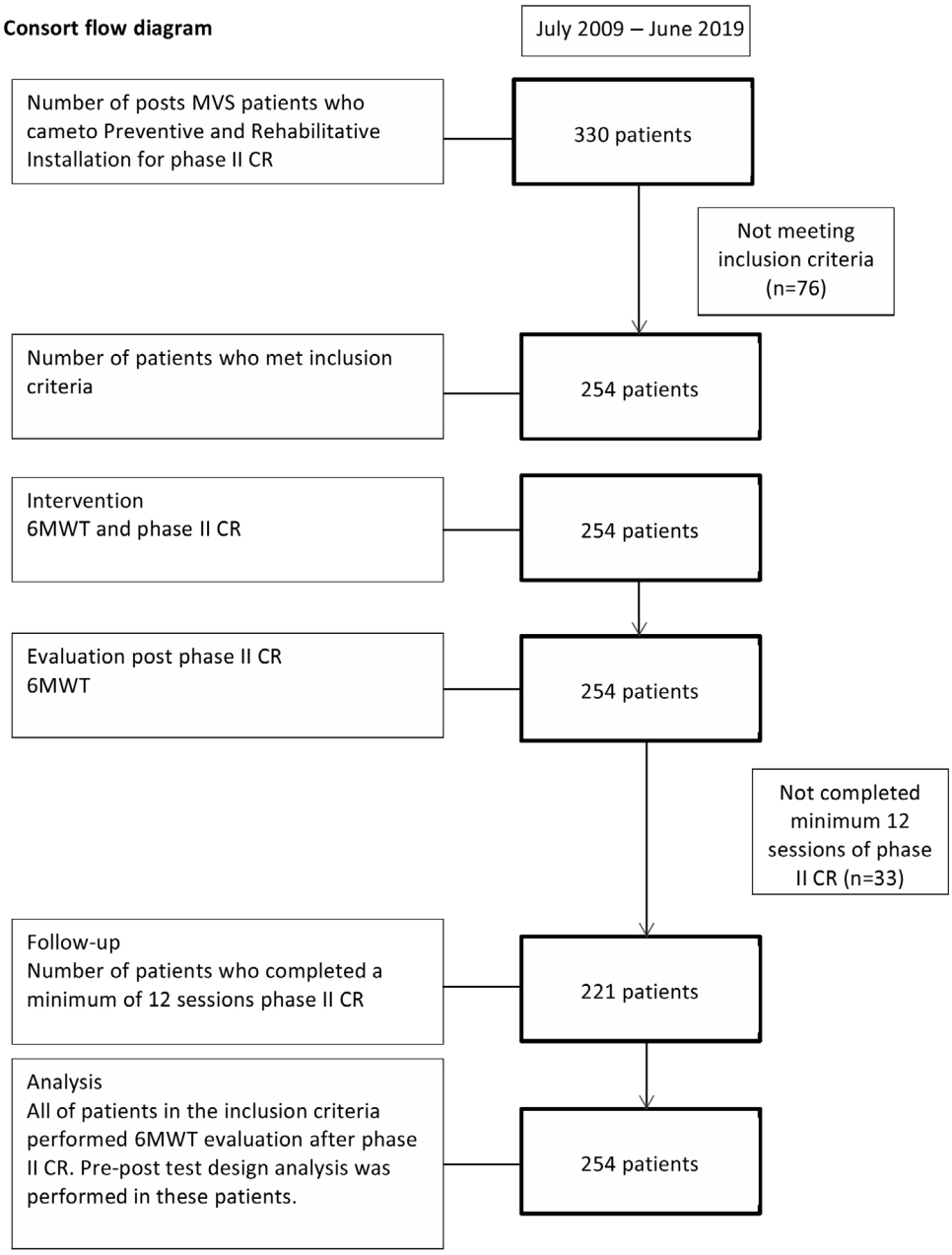



**Figure 2.** Mean of $VO_2$ peak in before and after phase II CR

**Table 2.** Correlation and Linear Regression of $VO_2$ peak Post as Dependent and 6MWD Post as Independent

| Variable | Coefficients B | r | $R^2$ | p value |
|---|---|---|---|---|
| 6MWD post | 0.027 | 0.715 | 0.511 | 0.001 |


Consort flow diagram
July 2009 – June 2019
Number of posts MVS patients who cameto Preventive and Rehabilitative Installation for phase II CR
330 patients
Not meeting inclusion criteria (n=76)
Number of patients who met inclusion criteria
254 patients
Intervention
6MWT and phase II CR
254 patients
Evaluation post phase II CR
6MWT
254 patients
Not completed minimum 12 sessions of phase II CR (n=33)
Follow-up
Number of patients who completed a minimum of 12 sessions phase II CR
221 patients
Analysis
All of patients in the inclusion criteria performed 6MWT evaluation after phase II CR. Pre-post test design analysis was performed in these patients.
254 patients

## DISCUSSIONS

Cardiac rehabilitation program is one of the effective methods for patients after mitral valve surgery to increase exercise capacity. Our study demonstrated that there was significant improvement of the exercise performance and peak $VO_2$ after the phase II Cardiac Rehabilitation Program (CR) ($p = 0.001$). 6MWT was used to describe the exercise performance of rheumatic heart disease patients after mitral valve surgery, and the peak $VO_2$ was calculated using Cahallin formula. 6MWT still becomes the easy and reproducible test yet reliable to describe the exercise performance and the functional capacity. Although the peak $VO_2$ was not directly measured using cardiopulmonary exercise testing (CPET), but the results of our study showed a strong correlation of the 6-minutes walking distance with the calculated peak $VO_2$. Our results were also in accordance with the other studies that investigated the functional capacity using the direct measurements of the peak $VO_2$. Pollmann et al[17] reported that patients who completed 12 weeks of CR increased their $VO_2$max ($21.6 \pm 8$ vs $24.8 \pm 9$; $p < 0.001$) and 6MWD ($349 \pm 110$ vs $393 \pm 121$; $p < 0.01$) whereas Savage et al[8] compared the effect of CR by dividing into 3 groups: mitral valve surgery (MVS), coronary artery bypass grafting (CABG), and mitral valve surgery combined with coronary artery bypass grafting. Results showed that all groups experienced an increase of $VO_2$peak especially MVS group ($17.2 \pm 5.1$ to 20.7 6.1; $p < 0.001$). Based on other clinical studies about CR after MVS, patients will lack confidence and difficulties to get on daily living after surgery so CR have good impacts for patients such as in their quality of life[18]. Sibilitz et al investigated 6MWD in 1 month and 4 months of patients with CR and not allowed to participate in CR by signing consents in this trial study. It showed patients that participated in CR has increased their 6MWD from 546.8 meters to 595.2 meters. Moreover, patients not allowed in CR programme has increased their 6MWD too from 542.9 meters to 594.5 meters[19]. Voller et al and Zanettini, et al compared 6MWD and found that mean difference of 6MWD patients at discharge test was significantly improved before at admission test[20,21]. Samples in this study were patients with transcatheter aortic valve replacement surgery. Both of those studies found that post CR patients with any types of surgery such as transcatheter aortic valve replacement or surgical

aortic valve replacement have significant improvements in 6MWD at admission and discharge test.

In rheumatic mitral stenosis patient, there had been a decrease in the functional capacity before the surgery, and there are several changes of hemodynamics after the surgery. Despite the improvements after mitral valve surgery, the functional capacity and the exercise performance of these patients were still far from normal; but near normal values of 6MWD and peak $VO_2$ in these patients were achieved after the early phase II CR.[22] A study from Russel et al[23] showed that there were no significant difference between the survival outcome of rheumatic vs non-rheumatic valve disease patients following mitral valve surgery. This study also explained that there were no difference of the survival outcome between the patients whose mitral valve were repaired and replaced. A similar results were found in our study that the types of the mitral valve surgery, whether it was repair or replacement, did not interfere the outcome of the exercise capacity improvement.

Our study used Cahallin formula to measure the peak $VO_2$, to predict the $VO_2$peak. Functional capacity is the ability to perform aerobic work as defined by the maximal oxygen uptake ($VO_2$peak), it reflects the ability to sustain the aerobic metabolism for daily activities. $VO_2$max is the product of cardiac output and arterio-venous oxygen difference at physical exhaustion.[24] Under physiologic conditions, the opening of the mitral valve during ventricular diastole will let the blood flow from the left atrium to the left ventricle, with the equal pressure in the left atrium and left ventricle. The presence of mitral stenosis in patient with RHD causes an impediment of the blood flow from the left atrium into the left ventricle, thus requires the atrial kick to flow the blood. The high left atrial pressure is then transmitted to the pulmonary vasculature that will lead to pulmonary hypertension. The sustainment of the high atrial pressure results in the increase of atrial size that will cause the diminishing of atrial kick. So, in the severe mitral stenosis with the loss of atrial kick, the cardiac output will also decrease.[25] Most patients with severe rheumatic mitral stenosis require surgical intervention, with the mitral valve repair or mitral valve replacement. The decrease of the cardiac output in these patients will cause the decrease in the functional capacity, alongside with the performance for their daily activities. Several physiological adjustments occurred after mitral

valve surgery, that also could influence the functional capacity and exercise performance. Luthra et al[26] reported early changes in pulmonary function after mitral valve surgery, that remained until 3 months after the surgery. There were reductions in forced vital capacity, forced expiratory volume in 1 second, and peak expiratory flow rates. This study also showed a reduction in the total lung capacity and diffusion capacity especially in patients with preoperative NYHA Class of III and IV. Bayat et al[27] demonstrated hemodynamic changes after mitral valve surgery in patients with or without pulmonary hypertension. This study showed that the pulmonary artery pressure was increased for approximately 3 mmHg immediately after the surgery, and then followed by a significant decrease for approximately 30mmHg in patients after undergoing mitral valve replacement and patients without pulmonary artery hypertension. Nevertheless, immediate reduction of the pulmonary artery pressure was not significant in perioperative mitral valve replacement that overt pulmonary artery hypertension; their pulmonary pressure decreased gradually depends on the severity. Another study showed unique findings; Jahns et al assessed the hemodynamic of post-mitral valve surgery patients at rest and during exercise using Doppler and catheterization. They showed that there was a postoperative decline in the pulmonary artery and pulmonary wedge pressure, but those declines did not reach the normal range. While the exercise was followed by a significant increase in cardiac output but pulmonary resistance remained unchanged. They suggested that these hemodynamic abnormalities were not a consequence of obstruction to flow across the valve prosthesis, but more likely due to only partial resolution of the pulmonary vascular bed because of the long-standing valve disease.[28] Therefore, although the overall patients with rheumatic heart disease had hemodynamic and physical capacity improvements, cardiac rehabilitation is still needed to sustain these improvements.

Our study performed the early phase II CR, which was 2 weeks after the surgery and consisted of 12 sessions of aerobic and resistance training, but by restraining the movements of the upper extremity. 13% of these patients did not complete the minimum of 12 sessions, but there were no inference to the 6MWD and survival outcome. Early phase II CR that was performed in our study (2 weeks after the surgery), because most of the patients from

many regions in Indonesia could not wait until 1 months to come back to their hometown or require more transportation fee to come back after 1 months. Our centre is a national cardiovascular centre, so the patients could come from any regions from Indonesia. Most of the patients who could not complete the minimum 12 sessions were because of the limitation to stay whether because of the accommodation fee or the urge to go back to their hometown. These outcomes were similar to the study from Meurin et al that performed the early exercise training 3 weeks after the mitral valve surgery.[29] Submaximal exercise test can be performed 2 weeks after surgery, while a symptoms limited (maximal exercise) test can be performed after 3-4 weeks.[30] Aerobic and resistance training could give stimulation to the human body to adapt and alter the resting physiological process, to meet the increased exercise-induced physiological demands. This process is characterized by significant changes in oxygen uptake and delivery to the exercising muscles accompanied by the increase of cardiac and pulmonary function in synchrony with the vasculature. Repeated exercise results in long term physiological adaptations which are essential to managing the requirements of repeated aerobic and resistance exercise, thus improving the physiological system involved in the exercise, such as the cardiovascular, metabolic, and respiratory systems.[31] Our study presents the importance of phase II CR following the mitral valve surgery in rheumatic heart disease patients. The limitation of this study is the indirect measurements of the maximal $VO_2$ to reflect the functional capacity, and this study is a pre-post test study without a control group to compare the effect of the early phase II CR. Although the measurement of the functional capacity was done indirectly using the Cahalin formula, this study showed a significantly strong correlation between the 6MWD and the $VO_2$peak. This result proved that 6-minutes walking distance measurement is an easy yet effective method to estimate the exercise performance and physical capacity. The lack of a control group was because only few patients refused to undergo the phase II CR.

## CONCLUSION

Early phase II CR in patients with Rheumatic Mitral Stenosis after mitral valve surgery improved the exercise capacity. Based on 6MWD, we can predict the value of $VO_2$peak patients with rheumatic mitral stenosis surgery patients.

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Chapter 5

# Randomised controlled trial into the role of ramipril in fibrosis reduction in rheumatic heart disease: the RamiRHeD trial protocol.

Ade Meidian Ambari, Budhi Setianto, Anwar Santoso, Basuni Radi, Bambang Dwiputra, Eliana Susilowati, Fadilla Tulrahmi, Annemiek Wind, Pieter A. Doevendans, Maarten-Jan Cramer

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## ABSTRACT

***Introduction*** Rheumatic heart disease (RHD) is a major burden in developing countries and accounts for 80% of all people living with the disease, where it causes most cardiovascular morbidity and mortality in children and young adults. Chronic inflammation and fibrosis of heart valve tissue due to chronic inflammation in RHD will cause calcification and thickening of the impacted heart valves, especially the mitral valve. This fibrogenesis is enhanced by the production of angiotensin II by increased transforming growth factor β expression and later by the binding of interleukin-33, which is known to have antihypertrophic and antifibrotic effects, to soluble sST2. sST2 binding to this non-natural ligand worsens fibrosis. Therefore, we hypothesise that ACE inhibitors (ACEIs) would improve rheumatic mitral valve stenosis.

***Methods and analysis*** This is a single-centre, double-blind, placebo-controlled, randomised clinical trial with a pre–post test design. Patients with rheumatic mitral stenosis and valve dysfunction will be planned for cardiac valve replacement operation and will be given ramipril 5 mg or placebo for a minimum of 12 weeks before the surgery. The expression of ST2 in the mitral valve is considered to be representative of cardiac fibrosis. Mitral valve tissue will be stained by immunohistochemistry to ST2. Plasma ST2 will be measured by ELISA. This study is conducted in the Department of Cardiology and Vascular Medicine, Universitas Indonesia, National Cardiac Center Harapan Kita Hospital, Jakarta, Indonesia, starting on 27 June 2019.

***Ethics and dissemination*** The performance and dissemination of this study were approved by the ethics committee of National Cardiovascular Center Harapan Kita with ethical code LB.02.01/VII/286/KEP.009/2018.

**Trial registration number: NCT03991910**

## INTRODUCTION

Rheumatic heart disease (RHD) is a serious health problem in developing nations, where it affects 80% of the population and accounts for the majority of cardiovascular morbidity and mortality in children and young adults. RHD affects more than 15.6 million individuals worldwide, with 233,000 people dying prematurely each year.[1] In the past 5 years, approximately 471 patients with rheumatic mitral stenosis were treated in our centre.[2] Treatments provided for RHD in advanced stages are relatively expensive for developing nations; thus, early detection and targeted treatment can greatly aid.[3] Mitral valve stenosis is the main presentation of RHD, commonly developing as a result of persistent or recurrent valvulitis with bicommissural fusion.[4] Fibrogenesis is induced by various stimuli, such as cytokines, connective tissue growth factors and activators. Previous studies suggest that RHD is an autoimmune disease that is associated with cytokine activation.[4] Inflammatory cytokines are key regulators of immune processes. Chronic inflammation causes damage to the valvular tissue. Many studies have investigated potential biomarkers to evaluate fibrosis and chronic inflammation processes in patients with RHD and ST2 is a sensitive marker for detecting cardiac fibrosis, including fibrosis progression in RHD.[4–6]

### Strengths and limitations of this study:

- A novel study that analysed the ST2 expression in mitral valves in patients with rheumatic heart.
- This study proposed novel and affordable treatment targeting the rheumatic heart valve fibrosis reduction.
- This research will help low-to-middle-income countries treat rheumatic heart disease more economically.
- Flexible schedule of mitral valve surgery causes different time range of the intervention for each patient.
- No standard healthy control of the non-fibrotic valve, based on ethical consideration.

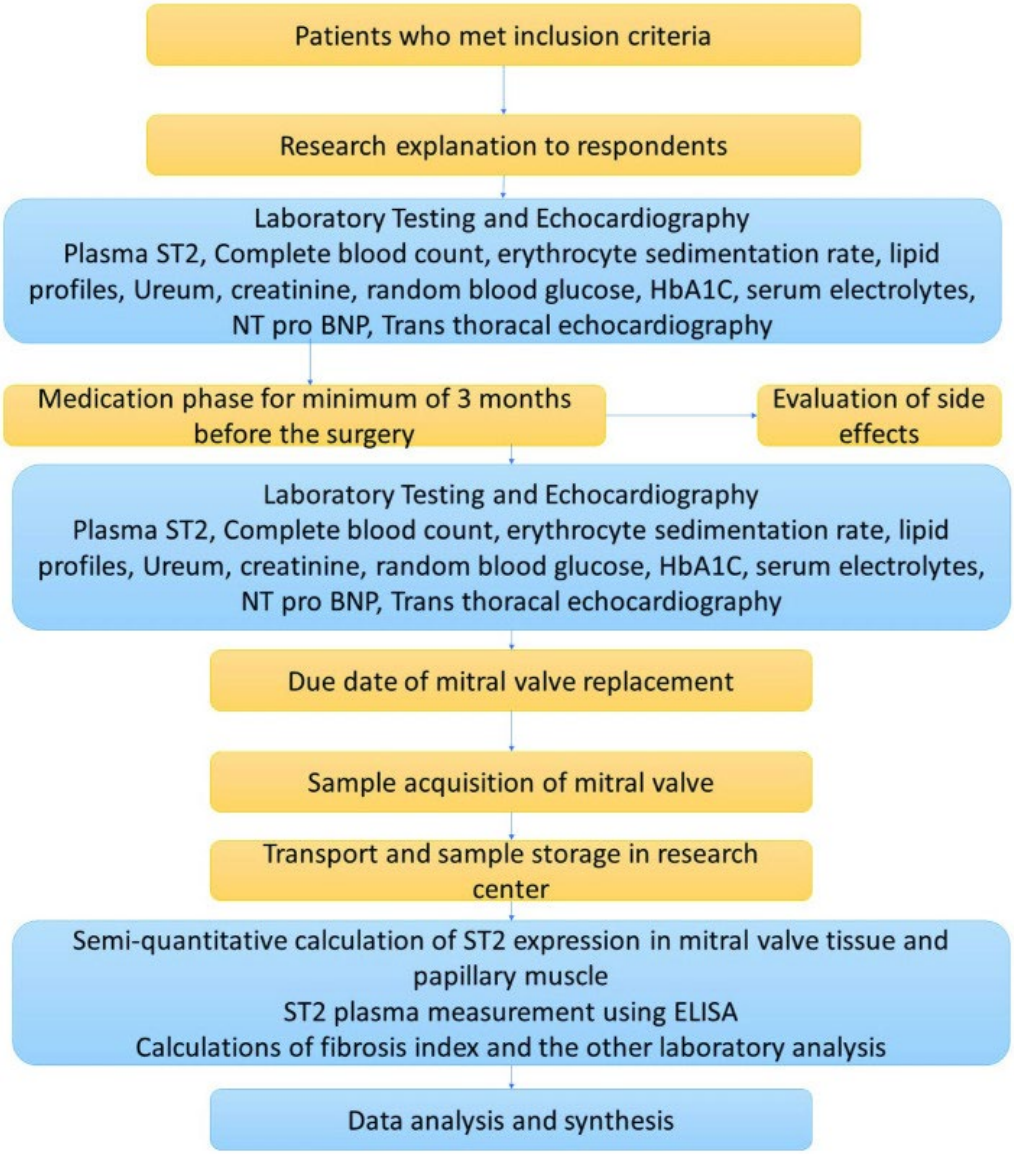


**Figure 1.** Hypothesis. Molecular mimicry is a defence mechanism of group A Streptococcus to avoid immune cells. This mechanism allows immune cells to generate autoimmunity against protein the lining of endothelial cells and causing chronic inflammation and valvular damage. Continuous process of chronic inflammation leads to valvular thickening and fibrosis, which is mediated by the angiotensin Angiotensin II increase TGF-β expression and cause IL- 33 to bind with sST2, and subsequently cause damage and fibrosis to the valvular tissue even more, which later will end with rheumatic heart failure. ACEI is hypothesised to counteract these processes by decreasing angiotensin II conversion from angiotensin I. ACEI, ACE inhibitor; IL, interleukin; TGF-β, transforming growth factor β.

ST2 is a member of the interleukin (IL)-1 receptor family discovered in a classical translational science fashion, and it exists in two forms: a transmembrane receptor (ST2L) and a soluble decoy receptor (sST2).[7] As a member of the IL-1 receptor family, ST2 is a biomarker of mechanical stress that is upregulated in isolated cardiomyocytes exposed to mechanical strain; derangement of ST2 signalling leads to a phenotype consistent with myocardial remodelling, and in patients with heart failure, sST2 levels strongly correlate with the severity of heart failure, independently forecasting risk on top of the risk from NT-proBNP and other biomarkers. Both sST2 and ST2L are induced in cardiomyocytes and fibroblasts exposed to biomechanical stress. Biomechanical stress and fibrosis will enhance valve thickening in RHD.[8] Clarifying the role played by ST2 in cardiovascular disease, IL-33 signalling through ST2L has been shown to have antihypertrophic and antifibrotic effects in the heart.[7] Calcification and thickening of the mitral valves are enhanced by the production of angiotensin II. Angiotensin II induces the upregulation of transforming growth factor β and later the binding of IL-33 to sST2 instead of its natural receptor ST2L. Binding of IL-33 to sST2 will cause fibrogenesis. Thus, ACE inhibitors (ACEIs) are hypothesised to attenuate this vicious cycle by inhibiting angiotensin II and consequently increasing bradykinin, which further inhibit fibrosis through the negative regulation of angiotensin II activity in mitogen-activated protein kinase pathways through the suppression of the Ca2 + response and Na + transport.[9,10]

ACEIs are frequently used to prevent and treat heart failure caused by regurgitant valve disease. Because of the risk of hypotension in the presence of a fixed obstruction, the majority of patients with symptomatic RHD have substantial mitral stenosis (MS) and refuse ACEI medication.[11] ACEI is the primary treatment for heart failure. The way ACEIs improve clinical symptoms and survival outcomes is to advance afterload reduction. Fibrosis attenuation and its antiproliferative effects and neurohormonal effects are superior to those of pure vasodilators.[11] Current guidelines for valvular intervention do not include ACEI as therapy in patients with rheumatic MS. The only established therapeutical options for rheumatic MS are balloon mitral valvuloplasty and mitral valve surgery (MVS). More economical therapeutical options that

target the inhibition of fibrogenesis and improve mitral valve fibrosis are needed, especially in low-income to middle-income countries. Valvular anti-inflammatory and anti-fibrotic medical therapy to slow the progression of the disease is needed in patients with rheumatic MS. One ACEI (enalapril) was well tolerated in symptomatic RHD associated with significant aortic and/or MS and preserved left ventricular systolic function.[11]

Currently, there is no treatment for rheumatic MS that targets the main pathogenesis, valvular fibrosis. Therefore, novel approaches and therapies are needed to prevent RHD progression.[4] Neutralising inflammatory cytokines or antagonising their receptor function has been considered a useful therapeutical strategy to treat autoimmune diseases.[4] In this respect, new therapies targeting ST2 and its ligands, as studied in some autoimmune diseases, may be a new approach for patients with RHD. ACEIs are agents with antifibrotic effects. This study therefore aims to investigate the effect of the ACEI ramipril in suppressing the expression of ST2 in the cardiac mitral valve in patients with RHD (figure 1).

## METHODS AND ANALYSIS

### *Study designs*

This is a single-centre, double-blind, placebo-controlled, randomised clinical trial with a pre–post test design. Patients with rheumatic MS with valvular dysfunction who are scheduled for cardiac valve replacement will be treated with ramipril 5 mg or placebo for a minimum of 12 weeks (3 months) before the surgery. ST2 will be checked as a fibrosis marker (figure 2). The study is still recruiting patients at the National Cardiac Center Harapan Kita Hospital, Jakarta, Indonesia, from 27 June 2019.

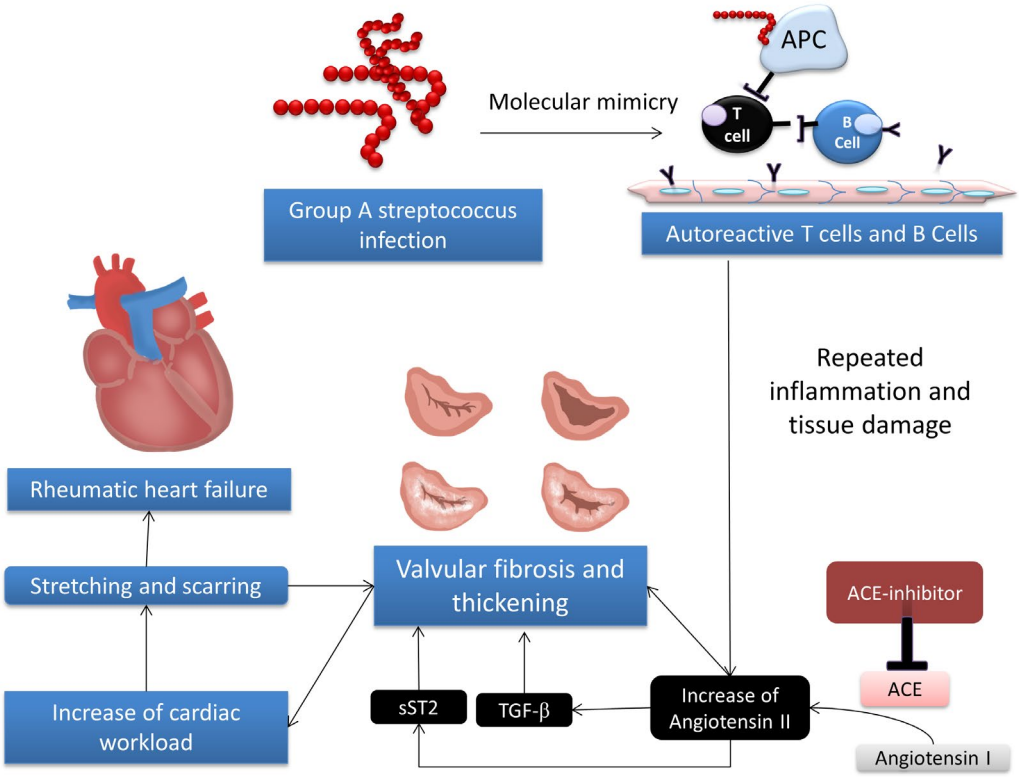


**Figure 2.** Research flowchart. TGF-β, transforming growth factor β.

## *Study population*

Patients with rheumatic mitral valve stenosis (RMS) who undergo cardiac valve replacement in the National Cardiovascular Center Harapan Kita (NCCHK), Jakarta, Indonesia, will be screened for eligibility. The inclusion criteria of this study are patients with RMS or combined valve disease aged more than 18 years who undergo cardiac valve replacement operation with or without tricuspid valve repair. Patients must also have systolic blood pressure (SBP) ≥100 mm Hg and diastolic blood pressure ≥60 mm Hg. The exclusion criteria of this study are patients with congenital heart disease, non-MVS, coronary artery bypass surgery or refusal to provide informed consent. Further exclusion criteria are adults aged 65 years or over, pregnant women and patients with autoimmune disease, persistent hypotension (SBP <100 mm Hg), severe aortic stenosis (aortic valve orifice <0.75 $cm^2$), chronic renal dysfunction with serum

creatinine >2.5 mg/ dL or known ACEI intolerance. Participants who meet the criteria and are willing to join the RamiRHeD trial will be informed in detail about the study and will be required to sign the informed consent.

### *Outcomes*

The primary outcomes of this study are the ST2 expression in mitral valve tissue and papillary muscle, and the secondary outcomes are soluble plasma ST2, clinical signs and symptoms that will be measured with the classification of NYHA (New York Heart Association), echocardiography results of: ejection fraction, TAPSE (tricuspid annular plane systolic excursion), end diastolic dimension, end systolic dimension, mitral valve area, mitral valve gradient, tricuspid maximal velocity and tricuspid regurgitation severity, as well as laboratory test results for NT-proBNP concentration. Study participants will be followed-up for cardiac and all-cause mortality outcomes until 1 year after the surgery.

### *Sample size and randomisation*

This is a pioneering study analysing the effects of 5 mg ramipril on ST2 expression in mitral valve tissue in humans. A previous study that used ST2 human tissue was conducted by Marzullo *et al* in 2016.[12] The used carotid tissue from carotid endarterectomy, with a sample size of 41 consecutive patients. Because our study will use human tissue samples, we approached the sample size calculation using the multistage non-finite population method, using this specified precision estimation formula[13]: $N=(Z\delta)/E$, with N=sample size; $Z_{0.95}= 1.96$; $\delta$ N(0,1)=1; and E=0.05 for a 0.95 CI. Therefore, we calculated a required sample of 1.65(1)/0.05=33 samples.

According to the sample size of the previous study that analysed ST in human tissue and a sample size formula that is commonly used in in vivo studies, we decided to use a sample size of 30 for each arm, and with the addition of a drop out rate of 10%, this became total of 66 for the two arms.

The number includes a 10% dropout and withdrawal from each group. Randomisation will be done with an equal ratio of ramipril to placebo. A computerised sequence generator is used for randomisation. It will be linked

with codes for placebo and treatment tablets provided by the manufacturer that was contracted to produce the trial medication. Researchers and participants will be blinded. After randomisation, the treatment pack and capsule will be identical between the two groups and will contain either active tablets or placebo. The principal investigator will have no access to the randomisation list.

## *Research technique*

The MVS will be mitral valve replacement. Echocardiography will establish the diagnosis of rheumatic mitral valve disease. Rheumatic valve disease will be diagnosed with World Heart Federation Criteria for RHD.[14] The reference measurement for valve area is planimetry by two-dimensional echocardiography. The Doppler technique is used to assess the mean mitral gradient. Seller's classification on left ventriculography in a right anterior oblique view angle of 30° will be performed to evaluate the severity of mitral valve regurgitation. In cases of missing data, substitution measurements will be used as previously described: Doppler half-time pressure for valve area and colour Doppler for mitral regurgitation.[14]

Patient classification and diagnosis of rheumatic MS will be determined by qualified cardiologists, and the decision to perform mitral valve replacement surgery will be based on the consensus of the multidisciplinary team, consisting of cardiologists and cardiothoracic surgeons. Echocardiography will be performed by echocardiography-consultant cardiologists. Blood samples will be collected by trained nurses specialised in pathology clinical laboratory work. Biomedical analysts will be in charge of the analysis and collection of ST2 in plasma and mitral valves. Detailed interviews with the study participants will be done by a well-trained medical doctor. The data will come from questionnaires, laboratory tests, echocardiography and biochemical tests. The study instruments will use the same technique, same tools, same brands and same place for data collection from each study participant.

Pre-existing atrial fibrillation, left atrial size, concomitant rheumatic valve disease, NYHA class and other clinical data and echocardiographic data will be documented before and after surgery and will be analysed by multivariate analysis.

### *Intervention*

Daily capsules containing 5 mg ramipril or placebo to be taken orally will be provided for the study participants. An initial dose of 2.5 mg of ramipril will be given to the patients in the intervention group. If there are no significant adverse effects documented in the first 2 weeks after the initial dose, 5 mg of ramipril will be given in the subsequent weeks until 5 days before mitral valve replacement surgery. Participants will remain under the care of the treating cardiologist team. The routine medications of each patient will be continued. Capsules containing 5 mg ramipril or placebo will be given for a minimum of 3 months, up until 5 days before the mitral valve replacement.

### *Withdrawal and drop out*

Participants will be informed that they will be able to withdraw from the study at any time and will sign a form stating this. They will be informed that this will not affect their clinical care. Basic clinical data and samples already collected will be included in the analyses in accordance with the consent obtained at trial entry. Drop-out criteria will be loss to follow-up, severe adverse events and mortality due to any cause.

### *Sample collection and measurements*

Clinical signs and symptoms will be documented before and after the study. Blood samples will be collected twice: before the intervention and 1 day before the MVS. The routine blood analysis will include haemoglobin, platelet count, leucocyte count, erythrocyte sedimentation rate and C-reactive protein. Total cholesterol, random blood glucose, HbA1c, urea, creatinine, serum electrolytes, NT-proBNP and plasma ST2 will be determined. Echocardiography before the intervention and before surgery will be performed. Mitral valve tissue expression of ST2 will be measured by immunohistochemistry (IHC). Plasma ST2 will be measured using an ELISA kit with the human ST2/IL-33R antibody (R&D Systems, catalogue number DST200). This assay uses the technique of the quantitative sandwich enzyme immunoassay. A monoclonal antibody specific for human ST2 is precoated onto a microplate. Standards and samples are pipetted into the wells, and any ST2 present is bound by the immobilised

antibody. Unbound substances are washed away and then, an enzyme-linked polyclonal antibody specific for human ST2 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells, and colour develops in proportion to the amount of ST2 bound in the initial step. After the colour development is stopped, the colour intensity is measured.

Mitral valve and papillary muscle tissue will be collected during mitral valve replacement surgery and will be saved in a sterile container filled with 10% formalin. ST2 expression will be observed using IHC. Cross-linking chemicals, such as paraformaldehyde and glutaraldehyde, will be used to preserve the cellular structure. The fixation begins when the tissue is harvested. Tissue blocking is performed afterwards by placing the tissue sample in hot parafilm, after which it is put into a mould until hard. Following fixation, tissue sections are obtained using a microtome. Decloaking methods consisting of heat and pressure treatment, enzyme digestion and microwaving are done afterwards. Following decloaking, the parafilm on the slides is removed by baking, and then the IHC staining process can be started. The primary antibody is a monoclonal ST2 antibody. The secondary antibody is conjugated by biotin. The blocking buffer includes BSA. The chromogen that will be used is 3,3'-diaminobenzidine (DAB). DAB oxidation is catalysed by horseradish peroxidase, after which it forms a brown precipitate, so ST2 expression can be visualised under a light microscope. The tissue will then be counterstained using H&E staining, so the non-ST2-expressing cells can be visualised in bluish colour. A negative control will use H&E staining only. Measurements of cells that express ST2 will be performed under a microscope. The date, tissue type, antibody dilution, tissue treatment and magnification of the microscope will be documented. ST2-expressing cells will be counted by more than one professional.

## *Statistical analysis*

Continuous variables are expressed as mean±SD, and categorical variables are expressed as percentages. The $x^2$ test will be used to see the relationship between dichotomous variables, and Student's t-test will be used for continuous variables. Single-variable correlation analysis and multivariable

linear regression analysis will be performed. A p value<0.05 is considered statistically significant. The analyses will be performed with SPSS (IBM Corp., Armonk, NY, USA) for Windows.

### *Ethics and dissemination*

The ethics of this study were approved by the ethics committee of NCCHK, Jakarta, Indonesia, with ethical code LB.02.01/VII/286/KEP.009/2018.

## DISCUSSION

This study is planning to recruit patients with rheumatic mitral valve to be randomised to obtain capsules containing either ramipril 5 mg or placebo. Rheumatic MS is the main presentation of RHD that leads to significant morbidity and mortality. Recurrent or persistent valvulitis with bicommisural fusion usually leads to MS. Previous studies suggest that RHD is an autoimmune disease that is associated with cytokine activities. Inflammatory cytokines are key regulators of immune processes.[4] Immunological reactions caused by autoreactive antibodies continuously cause chronic inflammation and valvular fibrosis, which can be detected by an increase in sST2, an emerging biomarker for cardiac fibrosis.[10,15,16]

IL-33 is the natural ligand of ST2 and is highly expressed in smooth muscles and airway epithelia.[17] An inflammatory state stimulates the upregulation of ST2 by some cells, such as keratinocytes and dermal fibroblasts, and mechanical strain upregulates ST2 in cardiac fibroblasts.[17,18] The soluble ST2 isoform is increased under inflammatory conditions such as sepsis, allergic asthma, trauma and pulmonary diseases.[19–22] Its elevation is also documented in some heart conditions, such as aortic stenosis and congestive cardiomyopathy, and this elevation is associated with the risk of heart failure and death.[23–27] In this study, plasma ST2 is considered an inflammatory and fibrotic biomarker of rheumatic MS. Because plasma ST2 can also increase in various conditions unrelated to cardiac fibrosis, this study also measures the ST2 expression in mitral valve tissue. Plasma ST2 describes the amount of ST2 in the circulation, whereas mitral valve cells that express ST2 describe the amount of transmembrane ST2.

ACEIs are commonly administered as the treatment of heart failure due to valvular regurgitation. Its use in MS is still debatable because of its hypotensive effect. A prior study assessing the safety of ACEIs in patients with MS showed that the ACEI enalapril was well tolerated and safe up to a dose of 10 mg two times per day.[11] ACEIs are presumed to have vasodilatory effects in obstructive lesions and will decrease systemic vascular resistance through arterial vasodilatation, thus increasing the transvalvular gradient. Their anti-remodelling effect is also well established, and their long-term use has also been proven to improve left ventricular ejection fraction in patients with systolic dysfunction.[28] Because a prior study[11] demonstrated the efficacy and the potential benefits of ACEIs in improving outcomes in patients with MS, this study aims to confirm and investigate the possible pathological mechanism of those improvements. This study will assess the effect of 5 mg ramipril as a cardiac antifibrosis treatment in patients with severe MS RHD. Their plasma ST2 concentrations will be compared. Plasma ST2 concentration will also be compared before and after several months of consuming 5 mg ramipril. There will be no healthy controls for this study because of ethical limitations in the acquisition of mitral valve tissue. Mitral valve tissue will be acquired during MVS. The expression of ST2 in mitral valve tissue will then be calculated semi-quantitatively and compared with the plasma ST2 results. It is hypothesised that ramipril will suppress the expression of ST2 in the cardiac mitral valve in patients with RHD.

In addition to the plasma ST2 level and the ST2 expression in mitral valve tissue, this study also compares the pre–post effects of 5 mg ramipril versus placebo on NT-proBNP concentration echocardiography strain parameters and clinical outcomes. Clinical signs and symptoms and echocardiography parameters have been evaluated in some studies of mitral valve stenosis, and showed that these were positively correlated with the NT-proBNP concentration.[29,30] This study will also compare the NT-proBNP concentration between patients receiving ramipril and placebo. We will also calculate the correlation between the NT-proBNP concentration and the ST2 plasma concentration and mitral valve expression.

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Chapter 6

# Adherence to Penicillin Treatment is Essential for Effective Secondary Prevention of Rheumatic Heart Disease : A Systematic Review and Meta-analysis

Ade Meidian Ambari, Basuni Radi, Bambang Dwiputra, Dean Arityanti, Thomas Rikl, Maria Patricia Inggriani, Eliana Susilowati, Estu Rudiktyo, Maarten J. Cramer, Pieter Doevendans, Budhi Setianto, Anwar Santoso,

*Submitted*

## ABSTRACT

**Background:** Penicillin has long been considered essential for the secondary prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). However, the incidence of ARF recurrence and RHD progression remain high, particularly in endemic countries. Thus, an evaluation of the effect of adherence to penicillin for secondary prophylaxis in reducing ARF recurrence and RHD progression is warranted. This meta-analysis aimed to evaluate the effect of adherence to penicillin for the secondary prevention of ARF recurrence and RHD progression.

**Methods:** We included original articles in which the study populations were patients with ARF or RHD, documented adherence to secondary prophylaxis with penicillin for secondary prevention. Systematic searching in PubMed, Scopus, and Cochrane were performed. The National Institute of Health (NIH) Quality Assessment Tool was used to assess the quality of each included study. Pooled odds ratios were used to compare different adherence methods.

**Results:** 292 papers were identified, of which forty four full-text articles were assessed for their eligibility. We included five studies with a total of 828 patients for qualitative synthesis and meta-analysis. Good adherence to penicillin in the secondary prophylaxis of ARF and RHD, significantly reduced the odds of ARF recurrence or RHD progression by up to 63% when compared to the poor adherence (pooled OR 0.37 [0.24–0.57]; $I^2$=0% [p=0.94]; Z = 4.54 [p < 0.00001]).

**Conclusion:** Good adherence to penicillin for secondary prophylaxis in patients with ARF or RHD is essential in reducing the risk of ARF recurrence or RHD progression.

**What is already known on this topic:**

For decades, penicillin has been used as the recommended secondary prevention agent against group A *Streptococcus* (GAS) infection that cause ARF and RHD. Nevertheless, the incidence of ARF recurrence and RHD progression remain high, particularly in endemic countries. Several studies

have suggested a correlation between poor adherence to penicillin as one of the culprits for high ARF recurrence and RHD progression incidence as well as the increasing rates of antibiotic resistance. The latest systematic review reporting adherence rates and variables related with adherence to secondary prophylaxis for ARF and RHD throughout the world was published in 2017.

**What this study adds:**

This meta-analysis evaluates whether good adherence to penicillin significantly contributes to the mitigation of ARF recurrence and RHD progression.

**How this study might affect research, practice, or policy:**

This study will provide reassurance for the use of penicillin as the secondary prevention for ARF and RHD based on the latest evidence. Moreover, adherence to penicillin therapy significantly affects the outcome of secondary prevention of ARF recurrence and RHD progression. Therefore, further policies in mitigating the ARF recurrence and RHD progression is necessary and should ensure the availability of penicillin regimens and address its compliance.

## INTRODUCTION

### Epidemiology of Rheumatic Heart Disease

Rheumatic heart disease (RHD) is a major global health burden, with RHD incidence continuing to rise in recent years. In 2017, approximately 38–40.8 million cases of RHD were observed worldwide,[1] with a significant discrepancy in the prevalence of RHD between endemic and non-endemic regions.[2] The prevalence of RHD is 3.4 cases per 100,000 people in non-endemic regions, whereas, in endemic areas, the prevalence has reached more than 1,000 cases per 100,000 people.[1] RHD is responsible for premature deaths of 0.15 per 100,000 children and an annual case-fatality rate per year of 1.5% among the global population.[1,3] Additionally, a high mortality rate of RHD has also been reported, with an average of 6–12% in highly endemic areas such as Ethiopia and Pakistan.[3]

In Indonesia, no recent integrated national data on the prevalence and incidence of RHD are available. In 1981–1990, the prevalence of RHD in Indonesia was 0.3–0.8 per 1,000 persons.[4] In Papua, 83 of the 15,608 mine workers were diagnosed with RHD.[5] A cardiac center in Bandung reported 108 out of 4,682 (2.3%) patients were diagnosed with RHD,[6] while the National Cardiovascular Centre Harapan Kita Jakarta, a national cardiovascular disease referral hospital in Indonesia, reported that RHD constituted 40.5% of the 7,112 valvular cases between 2016 and 2019.[7]

### Pathogenesis of RHD Progression

Antigenic mimicry causing autoimmunity, recurrent infection, inflammation, and streptococcal toxins have been proposed as the pathogenesis of RHD progression.[8] Due to the similarity of group A *Streptococcus* (GAS) with the M protein of several heart valvular proteins, the latter sometimes cannot be distinguished by B cells and T cells. This causes the generation of autoantibodies and heart tissue destruction, as well as the worsening of inflammation.[9] High recurrence rates of GAS infection and rheumatic fever (RF) are correlated with RHD progression.[10] Repeated inflammation by an autoimmune reaction further causes heart fibrosis, mediated by angiotensin II and transforming growth factor-beta (TGF-β). Angiotensin II enhances the fibrotic effect by stimulating

soluble suppression of the tumorigenesis-2 (sST2) decoy receptor, initiating the phosphorylation of c-Jun amino-terminal kinases (JNK) and extracellular signal-regulated kinases (ERK) in the mitogen-activated protein kinase (MAPK) pathway. This cascade of continuous inflammation and fibrosis results in a vicious cycle of heart damage caused by GAS infection in patients with acute rheumatic fever (ARF) and RHD.[9] Although most evidence outside of Oceania suggest that ARF develops primarily after nasopharyngeal GAS infection, it is increasingly recognised that GAS skin infections can also cause ARF.[11]

Penicillin antibiotics are administered to treat ARF and RHD. Intramuscular (IM) injection of benzathine penicillin G (BPG) is considered the first choice and the most effective option for preventing ARF recurrence.[12] Penicillin has been used for decades as a secondary prevention agent against GAS infections that cause ARF and RHD.[13] Secondary prevention is defined as the long-term administration of specific antibiotics to patients with prior ARF or well-documented RHD.[12] The European Society of Cardiology (ESC) guidelines for valvular heart disease in 2021[14] recommend secondary long-term prophylaxis for rheumatic fever using BPG 1.2 MUI every 3 to 4 weeks for more than 10 years. Lifelong prophylaxis is also recommended for high-risk patients according to the severity of valvular heart disease and exposure to GAS. Despite these well-known recommendations, the incidence of RHD remains a concern, especially in low- and middle-income countries.[1,15]

Previous studies have suggested a correlation between poor adherence to penicillin as one of the culprits for high RHD incidence.[16] Medication adherence often refers to whether or not patients take their drugs exactly as recommended, as well as whether or not they continue to take a given medication.[17] This concept suggests that the patient has a choice and that treatment objectives and a medical regimen are collaboratively established by patients and providers. However, supply and logistical issues can pose a serious threat for adherence, especially in low- and middle income countries. Resulting in one of the major current obstacles for effective ARF and RHD management.[18] A recent study[19] showed that proper prophylaxis is still important in patients with prior ARF. In this evolving landscape, the purpose of this meta-analysis was to assess the effect of penicillin adherence on the secondary prevention of ARF recurrence and RHD progression.

## METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements to perform this meta-analysis.[20]

### Eligibility Criteria

We included original articles in which the study population comprised patients with RHD who were diagnosed based on World Heart Federation or ARF by modified Jones criteria in which penicillin was administered as secondary prevention. The diagnostic criteria were assessed based on previous history of ARF or RHD in medical records or echocardiography-confirmed RHD. Secondary prevention includes IM BPG and oral penicillin antibiotics, considering access difficulty to BPG injection in some countries. Adherence to secondary prophylaxis was measured by minimum 12 injections per year or minimum 75% of scheduled doses taken. The outcome of the studies included should mention ARF recurrence or RHD progression. Non-original articles, such as systematic reviews, case reports, case series, and commentaries, were not included in the review. All original articles were in English and published between 2000 and 2022. Duplicate studies were removed.

### Search Strategy and Study Selection

Systematic searches in PubMed, SCOPUS, and Cochrane databases were performed. We used the identifying terms in all fields with : ("acute rheumatic fever" OR "ARF" OR "rheumatic heart disease" OR "RHD") AND ("secondary prophylaxis" OR "secondary prevention") AND ("adherence" OR "compliance") AND ("penicillin" OR "benzathine penicillin G"). A detailed search strategy can be found in Supplementary Table 1. The limit of the study publishing year from 2000 to 2022. Duplicated results were excluded. Five authors, AMA, ES, DA, TR, and MPI, independently screened the titles and abstracts of each original article, thoroughly read the full text of those articles, and discussed the selected articles together. The remaining investigators thoroughly read the full text of the selected articles and provided final suggestions. Finally, studies that were discussed and approved by the authors were included in qualitative and quantitative analyses. Any disagreements were resolved by consensus.

## Inclusion and Exclusion Criteria

We searched articles published in English between 2000 and 2022. The studies included should address patients with ARF or RHD who received secondary prophylaxis using oral or intramuscular penicillin in retrospective or prospective settings (cohort, case-control, trials). The exclusion criteria were non-original articles or case reports and when there was no data on the rates of adherence to penicillin. The expected outcomes were ARF recurrence, and/or RHD progression (patients with ARF who developed RHD or the worsening of RHD lesions) in patients with good or poor adherence. Studies which did not report the ARF recurrence or RHD progression will also be excluded.

Throughout the literature, there are various definitions of drug adherence. Patients having drugs available 80% of the time have been classified as adherent in the literature based on pharmacy refill data and it is considered reasonable in cardiovascular medications.[17] We purposefully used a cut-off of >70% adherence as our definition for inclusion because many institutions (including our own) use a >80% cutoff as a definition for good adherence for secondary prophylaxis for ARF. However, this prevented us from having to exclude studies that may have been relevant but used a lower cut-off percentage. This >70% includes both monthly IM and oral antibiotic administration.

Patients with ARF or RHD who were treated with penicillin for secondary prevention became the population in each study that is included in this analysis. Primary outcome was ARF recurrence. Acute rheumatic fever was defined based on the modified Jones criteria (World Health Organization [WHO] 2003 modification and rheumatic heart disease was diagnosed by the World Heart Federation, which facilitated the diagnosis of a primary episode of rheumatic fever (RF), recurrent attacks of RF in patients without RHD, recurrent attacks of RF in patients with RHD, rheumatic chorea, insidious onset rheumatic carditis, and chronic RHD).[12]

## Quality Assessment

The National Institute of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies[21] was used to assess the quality of the included studies. The NIH Quality Assessment Tool is used to analyze the risk of bias or methodological quality in observational studies. The NIH Quality Assessment

Tool for observational cohort and cross-sectional studies consists of 14 criteria assessing the study design, implementation, and results. Four authors, AMA, TR, DA, MPI and ES, assessed all of the included studies. The overall quality of the study was classified as good, fair, or poor, according to the investigators' agreement.

### Statistical Analysis

Dichotomous variables of ARF recurrence were used to calculate pooled odds ratio using the Mantel-Haenszel formula. Heterogeneity was assessed using Q statistics and $I^2$ tests by calculating the percentage of total variation across studies. The Q-statistic results of <0.05 and $I^2$ of 40% indicated heterogeneity across the studies. The random-effect model was used in this study to incorporate the possible expected heterogeneity between studies. A p-value of <0.05 were considered to be statistically significant. In a small number of studies, it has been observed that the DOI plot paired with the LFK index can more accurately identify publication bias. The publication bias was analyzed using DOI plot and LFK index (MetaXL, http://www.epigear.com) to assess its asymmetry. Statistical analysis was performed using RevMan 5.4.1.

## RESULTS

### Baseline Characteristics and Study Selection

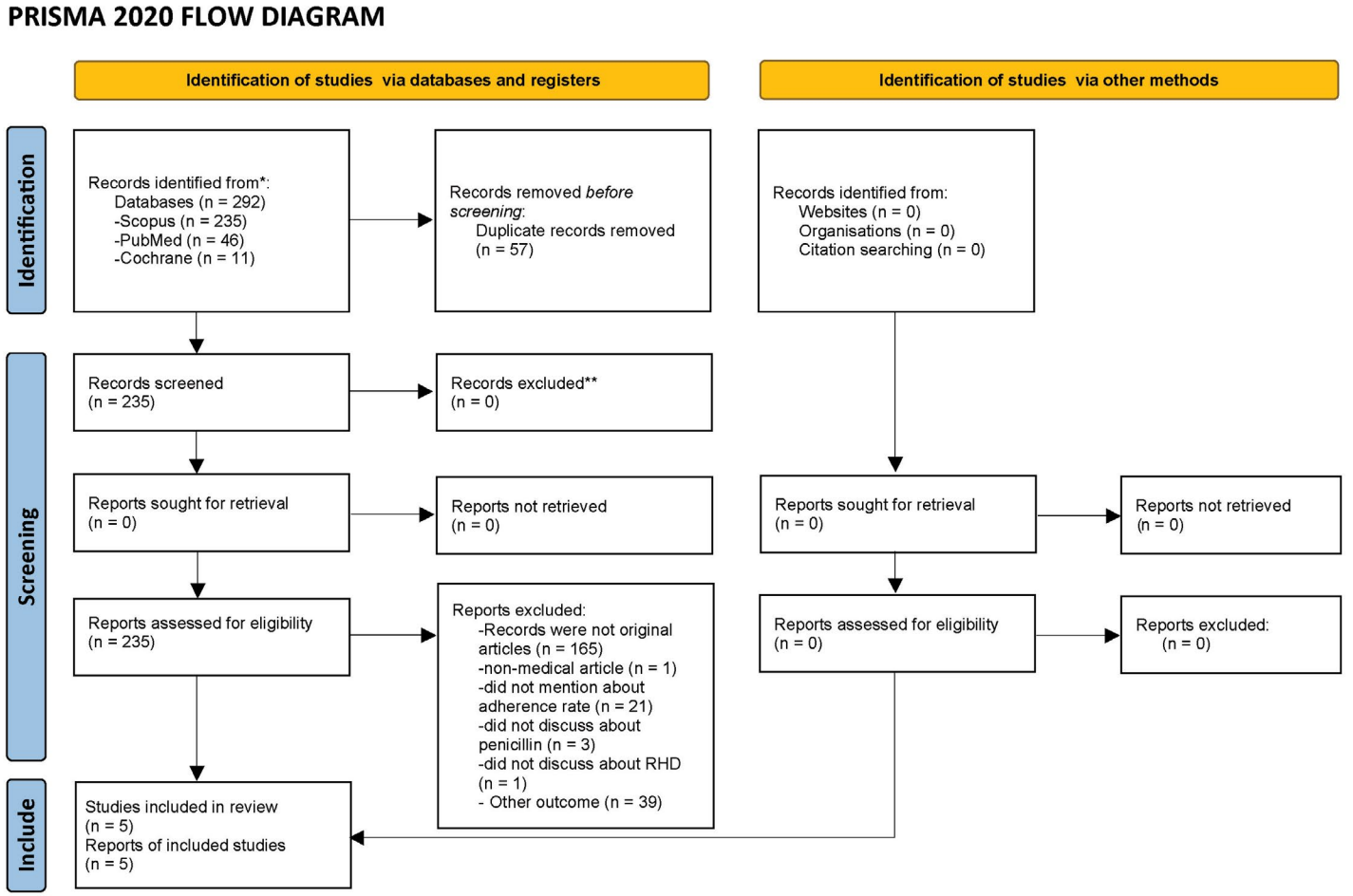
Our search between 20th January 2023 and 25th January 2023 retrieved a total of 292 studies from different databases. There are 235, 46, and 11 papers from Scopus, PubMed and Cochrane respectively. We screened the titles and abstracts of 235 studies after eliminating fifty seven duplicate studies and excluded 191 studies because they were neither original nor medical articles, did not discuss about penicillin or RHD, and did not mention about adherence in their abstract. Forty four full-text articles were assessed for eligibility, and thirty nine articles were excluded due to different outcome definitions. We therefore included five studies for qualitative synthesis and meta-analysis (Figure 1) with a total of 828 patients. The baseline characteristics of the included studies are summarized in Table 1. These five studies[22–26] were observational and BPG or oral antibiotics were administered to registered patients with a diagnosis of ARF or RHD for secondary prevention. The age of the population studied were ranging from 0 to >41 years old.

**Table 1** Baseline Characteristics of the Studies

| Authors | Country | Design | Study Population | Age | Samples (Good Adherence/ Poor Adherence) | Secondary Prophylaxis Regimens | Definition of Good Adherence to Penicillin as Secondary Prevention | Outcome | Median Follow-up Duration |
|---|---|---|---|---|---|---|---|---|---|
| Bassili *et al.*, 2000 | Egypt | Cross-Sectional | Children with RHD | 0 to 15 | 127 (82/45) | 2 weekly IM penicillin, 4 weekly IM penicillin, oral antibiotics | At least 11penicillin injections in the last 6 months or 22 injections during the last year of 2–4 weekly IM and daily oral penicillin | ARF recurrence | 4 months |
| Belay *et al*, 2022 | Ethiopia | Prospective cohort | Children with RHD | 5 to 17 | 272 (228/44) | 4 weekly IM penicillin or oral Amoxicillin | ≥80% IM penicillin (> 10 injections). For oral amoxicillin at least 80% doses per month (> 24 tablets per month in each of 12 months). | ARF recurrence, adherence to prophylaxis | 12 months |
| de Dassel *et al.*, 2018 | Australia | Case Crossover | People living in the NT with a history of ARF or RHD | 0 to >41 | 116 (15/101) | 3 weekly IM penicillin, 4 weekly IM penicillin | ≥80% IM penicillin at least 6 | Streptococcal colonisation, and infection or fever | 12 months |
| Haran *et al.*, 2018 | Australia | Prospective Cohort | Patients diagnosed with ARF or RHD from 2010 to October 2013 | 5 to 16 | 23 (16/7) | 4 weekly IM penicillin | ≥75% IM penicillin scheduled doses | Echocardiographic RHD progression | 27 months |
| Taddio *et al*, 2019 | Italy | Retrospective Cohort | Patients with ARF from 2000 to 2015 | Not Recorded | 290 (215/75) | IM Penicillin (Intervals not stated) | IM penicillin injections > 12 injections per year | ARF recurrence, presence of RHD | 4 years |

BPG: Benzathine penicillin G; ARF: Acute Rheumatic Fever; NT: Northern Territory

**Figure 1.** PRISMA study flow diagram



## Adherence measurements

There were various definitions of good adherence used in these studies. The articles from de Dassel et al.[24] and Belay et al.[23] defined good adherence as patients who received at least 80% of penicillin injection doses, while Haran et al.[26] defined it as patients who received at least 75% of the scheduled doses. Bassili et al.[22] defined it as at least 11 penicillin injections in the last 6 months or 22 injections during the last year of 2–4 weekly IM and daily oral penicillin, whereas Taddio et al.[25] defined it as >12 penicillin injections per year.

## Outcomes of the Included Studies

All studies reported ARF recurrence or RHD progression as the outcome.[22–26] Both Haran et al.[26] and Taddio et al.[25] reported the outcome as RHD progression in ARF patients, Bassili et al.[22] and Belay et al.[23] reported ARF recurrence as the outcomes, while de Dassel et al.[24] reported both ARF recurrence and RHD progression as the study outcome.[27]

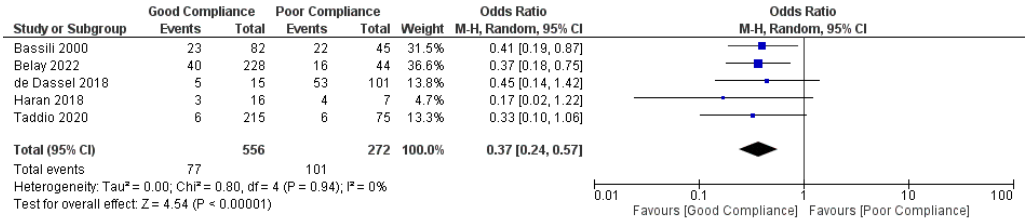
## Adherence to Penicillin for Secondary Prevention and ARF Recurrence

A total of 556 patients were considered as having good adherence, while 272 patients were considered having poor adherence. The prevalence of good adherence to penicillin for secondary prophylaxis varied in each study, ranging from 12.9% to 83.8%.[22–26] Most of the included studies (two studies from Australia and one study from Ethiopia) defined adherence to penicillin treatment as minimum taking 75% to 80%[23,24,26] or more of not missing penicillin administration or receiving more than 10 doses of penicillin shots per year.[22,25] Adherence to oral antibiotics was defined as receiving daily doses for the last 6 months or completing at least 80% of the prescribed doses each month.

There is a significant association between good adherence to penicillin administration for the secondary prevention of ARF recurrence and RHD progression in patients with ARF or RHD. Good adherence to penicillin administration significantly reduced the odds of ARF recurrence and RHD progression by up to 63% compared to the poor adherence (pooled OR 0.37 [0.24–0.57]; $I^2$=0% [p=0.94]; Z=4.54 [p<0.00001]) (Figure 2). In other words, when the patients with ARF or RHD had poor adherence to penicillin secondary prophylaxis, the odds

of having ARF recurrence or RHD progression were approximately three times higher compared to when they had good adherence to penicillin.

**Figure 2.** Forest plot on good adherence to penicillin as secondary prevention of ARF recurrence and RHD progression




## Mode of administration

Penicillin for secondary prevention is administered by injection or oral regimen. All of the studies[22–26] showed the beneficial effects of penicillin for secondary prevention of ARF and RHD despite different intervals of injections, ranging from 2 to 4 weeks. Two of the studies[22,23] administered either penicillin injection or oral penicillin. In patients who did not have access to IM penicillin, owing to a lack of medication availability or a lack of skilled individuals to give the injection in their location, Belay et al.[23] used amoxicillin, instead of penicillin V, as secondary prophylaxis for RHD. Although amoxicillin is indicated for primary ARF prevention, there have been no trials on its usage as secondary prophylaxis. When available, the suggested prophylactic medication is penicillin V rather than amoxicillin. Amoxicillin was prescribed due to the unavailability of penicillin V in Ethiopia.[23]

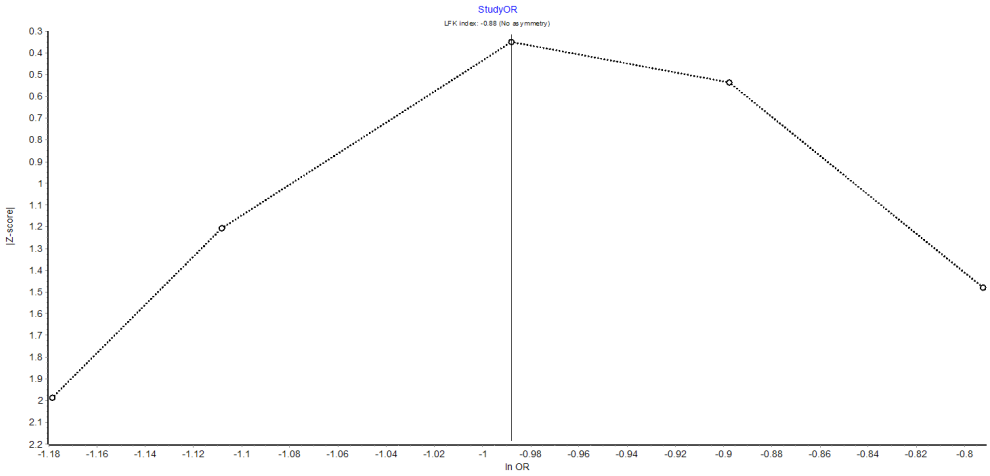
## Quality Assessment

Quality assessment of the included studies showed that most of the studies had good overall quality (five studies) (Supplementary Table 2). The sample size of the included studies displayed a large variation, from the lowest sample size (23 subjects) to the highest sample size (290 subjects) (Table 1). Studies by Bassili et al.[22], de Dassel et al.[24], and Haran et al.[26] had a loss to follow-up of less than 20%, while Taddio et al.[25] had a loss to follow-up of >20%. Unfortunately, Belay et al.[23] did not report the loss to follow-up number after baseline (Supplementary Table 2).

## Publication Bias

Our study showed a LFK index of -0.88 (Figure 3), whereas the LFK index below ±1 was considered no asymmetry, between ±1 and ±2 was considered minor asymmetry and exceeds ±2 was considered major asymmetry in the DOI plot.[28] Despite the DOI plot and LFK index showed no asymmetry, the studies included were very limited. Therefore, we cannot exclude publication bias in this meta-analysis.

**Figure 3.** DOI plot analysis




## DISCUSSION

The main finding of this meta-analysis is that good adherence to penicillin is crucial to prevent further complications after ARF and RHD. Although the early course after ARF is mainly asymptomatic, 60% of individuals do acquire carditis with persistent valve damage known as RHD if appropriate prohylaxis is not initiated.[11] Therefore, initiation and adherence to its therapy is lifesaving but also difficult in the absence of notable symptoms in the early phases of the disease.

The risks of ARF recurrence will be decreased by 17% for every 10% improvement in adherence.[24] The recent randomized controlled trial by Beaton et al.[19] showed that secondary prevention using penicillin injection every 4 weeks significantly lowered the risk of RHD progression in the current era, which

shows that penicillin is still the appropriate therapy in this patient population, despite other reports of potential antibiotic resistance in these populations.

Our study suggested that also in real-life data (which is not always comparable to trial data) more than 60% of ARF recurrence and RHD progression can be halted by having good adherence in taking penicillin as secondary prevention of ARF and RHD. Therefore, we believe that this meta-analysis may become additional consideration for health policymaking towards ARF and RHD patients.

## Adherence to Penicillin for Secondary Prevention of ARF and RHD

Majority of the studies addressing adherence to secondary prevention to ARF or RHD defined 'good adherence' as taking more than 80% scheduled doses of penicillin injections.[23,24] One study[26] described taking more than 75% scheduled doses as the cut-off for 'good adherence'. Some others[22,25] defined 'good adherence' by the minimal number of injections taken over some period of time. Personally, in Indonesia, we prefer using the 80% cut-off for good adherence. First, most of the studies assessing 'adherence' in secondary prevention of ARF or RHD used 80% as the cut-off point and more 'universal' (not only applied in secondary prevention of ARF or RHD) and reasonable in cardiovascular medications.[17] Thus, it is rational that the cut-off point was supported with more robust evidence. Second, the definition of good adherence by the minimal number of injections taken over some period of time usually uses different cut-off points. Therefore, it might be problematic when comparing the results.

## Factors Associated with Adherence to Penicillin for Secondary Prevention of ARF and RHD

Poor medication adherence is frequently complex. Medication noncompliance might be intentional or unintentional. Intentional nonadherence is a deliberate procedure in which the patient chooses to depart from the treatment plan. This might be a logical decision-making process in which the individual assesses the risks and advantages of therapy against potential negative consequences. Unintentional nonadherence is a passive process in which the patient is negligent or forgetful about following the treatment schedule.[17]

A qualitative study using focused-group discussion among RHD patients reported several factors of poor adherence to penicillin prophylaxis, especially in developing countries, including the lack of knowledge and perception of streptococcal pharyngitis, ineffective treatment strategies, and barriers to reaching healthcare services. Community awareness and confidence in the healthcare system as well as the cost of medication and indirect costs also need to be improved to increase penicillin adherence in patients with ARF and RHD.[29]

A systematic review, using published studies between 1994 and 2014, by Kevat et al.[18] reported several factors associated with patient's adherence to secondary prevention of RHD. Non-adherence was shown to be more widespread among youngsters in semi-urban and rural locations.[22] Adherence may be reduced by lack of faith in the therapy, lack of the sense of "belonging" to the health provider, and lack of family support.[18] In rural places, the availability of health personnel was limited, and participants had to make significant efforts to receive health care from alternative sites. Lack of a method for alerting individuals when their needles were due was one factor contributing to low compliance.[30] The presence of health professionals who had close, long-term interaction with the participants and an interest in preserving compliance might have a favorable influence on compliance.[30] Longenecker et al.[31] suggested that improving retention in treatment, potentially through decentralization of RHD services, would have the largest influence on antibiotic prophylaxis use among RHD patients. All of the above should be considered to continuously improve adherence in these populations.

Obesity was linked to increased secondary prophylaxis compliance. It was hypothesized that BPG injections hurt more for individuals with lower body mass index (BMI) than for those with higher BMI.[24] Hence, developing a more comfortable technique for injecting penicillin may also increase the adherence to secondary prophylaxis.

## Injection versus Oral Administration of Penicillin

Although taking oral penicillin is more practical for patients, administering penicillin by injection makes it simpler to monitor and guarantee compliance. As a result, the improved results linked to injections may be explained by

patients being more likely to follow their recommended treatment schedule.[32] However, it should be kept in mind that administering penicillin for secondary prophylaxis via injections may be costly and yet become ineffective in areas which have difficult access to healthcare. To our knowledge, there is no study that compared oral administration of penicillin versus injection for the outcome of ARF recurrence or RHD progression.

## Global Situation

Globally, RHD affects around 40.5 million individuals, while 306,000 people die each year from its consequences.[19] Secondary prophylaxis with intramuscular penicillin injections on a regular basis is an important component of ARF and RHD management regimes.[18] The World Health Organization (WHO) advises 3-4 weekly BPG for a period of time determined by parameters such as age, time since the previous episode of ARF, risk of streptococcal infections in the area, and the existence of RHD. Secondary prophylaxis should be continued for at least 5 years after the last episode of ARF or until the age of 18 years (whichever is higher), and for a longer period of time in cases of carditis or RHD.[12] Generally, ARF recurrence is diagnosed using the widely accepted revised Jones criteria.[33] RHD diagnosis and progression were based on the World Heart Federation criteria of 2012.[27]

Subclinical RHD develops 5-15 years before clinical signs of RHD in its natural history phase. RHD's extended latent period provides a chance for prevention before the illness manifests clinically. The World Health Organization (WHO) advises screening as an effective method of detecting the disease at an early stage so that secondary prophylaxis may be provided to individuals who would benefit the most.[34]

## Local Situation in Indonesia

Likewise, in Indonesia, the recurrence of ARF and RHD was strongly associated with non-adherence to penicillin as secondary prophylaxis. There are limited data regarding adherence to penicillin secondary prevention in ARF and RHD in Indonesia. A study showed that the average adherence to penicillin secondary prophylaxis was 48.8% in children with ARF and RHD, with the recurrence of ARF or RHD being six times higher compared to those who were adherent

(p=0.016).[35] To date, no study in Indonesia has reported the determinants of poor adherence to secondary penicillin prophylaxis in ARF and RHD.

Data from a national cardiovascular center in Indonesia demonstrated that RHD recurrence mostly manifested in carditis (66.7% in children and 61.9% in young adult patients), 62.5% of patients had elevated ASO titers, and 35.1% had a positive throat culture of BHS. Among the children and young adults with RHD recurrence admitted to this cardiac center, 59.1% underwent heart valve surgery and 27.5% underwent percutaneous balloon mitral valvuloplasty. The patients were followed up for adherence to penicillin secondary prevention, and one patient with good adherence to a 1-year period of secondary prophylaxis developed RHD reactivation 4 years later.[36]

## Limitations

A limitation of this meta-analysis was the limited number of studies which addressed the compliance of secondary penicillin prophylaxis on the recurrence of ARF. First, all the included studies were published in English and we did not incorporate other evidence published in different languages. The DOI plot indicated that in our study there was low chances of publication bias as detected as no asymmetry according to its LFK index. However, we cannot exclude any publication bias due to very limited number of studies included. Second, included studies were of different study setups and all observational with significant heterogeneity in each study, particularly in the study population. Therefore, the conclusion of this study should be adjusted in the setting of respective medical practices and also the clinical judgment from health care providers.

## Future Direction

A multimodal strategy is necessary for the prevention and management of ARF and RHD, including early diagnosis, efficient treatment, and increased prophylaxis adherence. A greater focus on enhancing the health system is necessary to improve adherence to secondary prophylaxis for ARF and RHD. This entails enhancing the accessibility and availability of antibiotics, educating healthcare professionals in effective counseling and communication techniques, and making sure that treatment programs are adequately monitored

and evaluated. In the fight to halt the burden of ARF recurrence and RHD progression, promoting adherence to secondary prophylaxis is a crucial topic for future study and intervention. Therefore, we underlined the significance of improving penicillin compliance as the secondary prophylaxis in patients with ARF and RHD based on data over the last two decades.

## CONCLUSION

Good adherence in secondary prophylaxis using penicillin, regardless the methods of administration, in patients with ARF or RHD is essential in preventing ARF recurrence or RHD progression. Thus, further regulations are required to mitigate the advancement of RHD and ARF, and they should guarantee the availability of penicillin regimens and address its compliance.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None.


## COMPETING INTERESTS

The authors have no competing interests to declare.

## AUTHORS' CONTRIBUTIONS

The conception or design of the study was initiated by AMA, BS, AS, BR, BD, PD, and MJC. A systematic search was performed using AMA, ES, DA, TR, and MPI. Data were extracted by AMA, ES, DA, MPI, and TR, under the supervision of the MJC. Quality assessment of the studies was discussed by AMA, TR, DA, and ES under the supervision of MJC. AMA, ES, DA, TR, and MPI drafted the manuscript. AMA, BS, AS, BR, BD, PD, and MJC critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy. AMA is the guarantor and responsible for the overall content of this study.

## Supplementary Table 1. Result from Database Search

| Keyword | Search Engine | | |
|---|---|---|---|
| | PubMed (20th January 2023) | Scopus (22nd January 2023) | Cochrane (24th January 2023) |
| ("acute rheumatic fever" OR "ARF" OR "rheumatic heart disease" OR "RHD") | 16,932 | 101,011 | 24 |
| ("acute rheumatic fever" OR "ARF" OR "rheumatic heart disease" OR "RHD") AND ("secondary prophylaxis" OR "secondary prevention") | 276 | 1,273 | 21 |
| ("acute rheumatic fever" OR "ARF" OR "rheumatic heart disease" OR "RHD") AND ("secondary prophylaxis" OR "secondary prevention") AND ("adherence" OR "compliance") | 75 | 413 | 15 |
| ("acute rheumatic fever" OR "ARF" OR "rheumatic heart disease" OR "RHD") AND ("secondary prophylaxis" OR "secondary prevention") AND ("adherence" OR "compliance") AND ("penicillin" OR "benzathine penicillin G"). | 46 | 235 | 11 |

## Supplementary Table 2. Quality assessment of the included studies

| Criteria | Bassili *et al.*, 2000 | | | Belay *et al.*, 2022 | | | de Dassel *et al.*, 2018 | | | Haran *et al.*, 2018 | | | Taddio *et al.*, 2020 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | Other (CD, NA, NR)* | Yes | No | Other (CD, NA, NR)* | Yes | No | Other (CD, NA, NR)* | Yes | No | Other (CD, NA, NR)* | Yes | No | Other (CD, NA, NR)* |
| 1. Was the research question or objective in this paper clearly stated? | ✓ | | | ✓ | | | | ✓ | | ✓ | | | ✓ | | |
| 2. Was the study population clearly specified and defined? | ✓ | | | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| 3. Was the participation rate of eligible persons at least 50%? | ✓ | | | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | ✓ | | | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | | ✓ | | ✓ | | | ✓ | | | | ✓ | | ✓ | · | |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | | | NA | ✓ | | | | · | NR | | ✓ | | | ✓ | |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | | | NA | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | ✓ | | | | · | NR | ✓ | | | ✓ | | | ✓ | | |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | ✓ | | | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| 10. Was the exposure(s) assessed more than once over time? | | ✓ | | | ✓ | | | | NR | | | NR | · | ✓ | |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | | ✓ | | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| 12. Were the outcome assessors blinded to the exposure status of participants? | | · | NR | · | ✓ | | | | NR | | | NR | | ✓ | |
| 13. Was loss to follow-up after baseline 20% or less? | ✓ | | | · | | NR | ✓ | | | ✓ | · | | | ✓ | |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | | ✓ | | ✓ | | | ✓ | | | | ✓ | | ✓ | · | |
| Overall** | Fair | | | Good | | | Good | | | Good | | | Good | | |

*CD, cannot determine; NA, not applicable; NR, not reported
** Good, Fair, Poor

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# Chapter 7

## General discussion and future perspectives

## Final synthesis: Summary

### Introduction

The prevalence of rheumatic heart disease (RHD) is significantly high in middle- and low-income nations, particularly among young individuals. Data on the RHD burden were published by the Global Burden of Disease study (2016). In 2015, global RHD prevalence rates were greater than those of tuberculosis, and RHD was estimated to affect approximately 33.4 million individuals worldwide.[1]

Recurrent acute rheumatic fever (ARF) can affect cardiac valves secondary to an inflammatory response to group A Streptococcus (GAS) infection. An autoimmune response against the M protein in the subendothelial collagen matrix is implicated as the pathogenetic mechanism underlying RHD following GAS infection. The autoimmune reaction leads to recurrent inflammation and consequently chronic inflammation, neovascularization, and fibrosis. Valvular fibrosis and thickened heart valve leaflets serve as the primary drivers of RHD progression and increase the cardiac workload, which consequently causes cardiac stretching and scarring, which triggers further heart valve and myocardial fibrosis and scarring and ultimately a decline in ventricular function.[2]

RHD is associated with various structural abnormalities and usually affects the left-sided heart valves. Regurgitant lesions are more common in young patients, and older patients usually develop mixed or stenotic lesions. RHD of the mitral valve (MV) is morphologically characterized by thickening of the MV leaflet tips, chordal thickening, excessive leaflet tip motion, and limited leaflet motion. Valvular thickening is most pronounced at the leaflet tips.[3]

Rheumatic MV abnormalities typically present with valvular thickening, commissural fusion, subvalvular apparatus thickening, and chordal shortening. Mitral stenosis (MS) is characterized by diastolic doming and a "hockey stick" appearance of the anterior MV leaflet. Mitral regurgitation (MR) occurs secondary to asymmetric leaflet tethering and decreased coaptation; however, chordal rupture with a flail leaflet can also precipitate MR.[4]

Rheumatic mitral stenosis (RMS) is defined as a mitral valve area (MVA) measuring <1.5 cm2 with thickened or calcified valves. Transthoracic echocardiography (TTE) is considered the gold standard for diagnosis, assessment of the severity, evaluation of heart function, planning for intervention, and evaluation of RMS while transesophageal echocardiography (TEE) also an a crucial adjuvant to look for more precise evaluation of the mitral valve morphology.[5–8] Further imaging using TEE is performed for evaluation of thrombosis and to confirm valvular anatomy in patients in whom TTE provides inadequate information. The measurements between TTE and TEE should be synchronize and giving a validated range of mitral valve pathologies.[9]

Interventional treatment is recommended in clinically relevant RHD in patients with moderate-to-severe MS with an MVA of <1.5 $cm^2$.[10] Usually, patients with mild-to-moderate MV calcification or subvalvular apparatus injury can undergo percutaneous balloon mitral valvuloplasty (PBMV) in the absence of contraindications, including severe MR, extensive calcification, persistent thrombus in the left atrium (LA) and/or the LA appendage, severe aortic valve disease, tricuspid stenosis/regurgitation, and coronary artery disease that requires bypass grafting. Surgery remains an option in cases of PBMV failure or in those with contraindications for PBMV. Diuretics, beta-blockers, digoxin, non-dihydropyridine calcium channel blockers, and ivabradine are indicated for symptomatic relief of RMS and penicillin for secondary prophylaxis of GAS infection to avoid recurrent ARF. However, these drugs do not delay progression of fibrosis or inflammation in RMS. RHD is more common in middle- to low-income nations with limited access to healthcare. Affordable drug options to reduce inflammation and heart valve fibrosis are warranted in this patient population.

We addressed four main questions in this thesis (Figure 1).

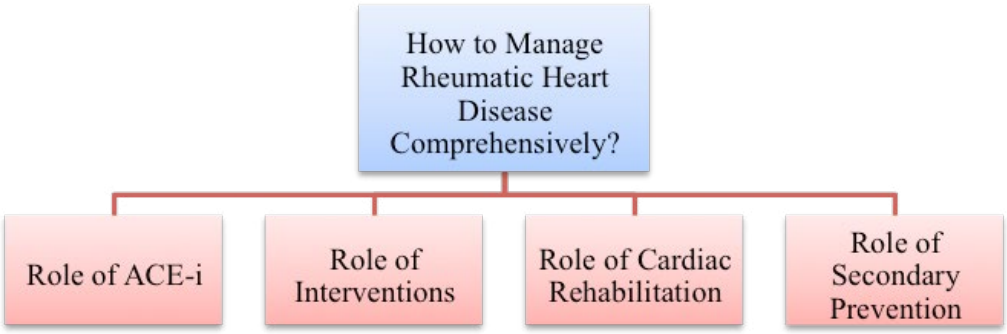


**Figure 1**. Thesis questions for the management of rheumatic heart disease

## Molecular basis for angiotensin-converting enzyme inhibitor use in attenuation of heart valve fibrosis in rheumatic heart disease

Persistent inflammation and autoimmunity triggered by the GAS antigen result in gradual deterioration of heart valves and tissue fibrosis. The consequent heart valve thickening and calcification increase cardiac workload and lead to a decline in cardiac function. In Chapter 2, we present detailed literature analysis of the potential role of angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of RHD and reduction of valve fibrosis caused by the suppression of tumorigenicity (ST2) receptor.[11–16] GAS infection triggers recruitment of immune cells and release of pro-inflammatory cytokines.[17,18] B-cells respond by producing autoantibodies because the amino acid sequence and structural conformation of self-antigens are identical. These autoantibodies cause extracellular matrix (ECM) and fibroblast deposition and myofibril contraction via activation of adhesion molecules and upregulation of growth factors, cytokines, and immune cell recruitment.[19]

The levels of angiotensin II and soluble ST2 (sST2), which function as decoy receptors, are also increased under inflammatory stress and they activate pathways that promote fibrosis. Transforming growth factor (TGF) triggers connective tissue growth factor, matrix metalloproteinase, tissue inhibitor metalloproteinase expression, cellular adhesion, fibroblast proliferation, and ECM buildup.[20] Angiotensin II stimulates TGF via activation of mitogen-activated protein kinase/c-Jun N-terminal kinase (MAPK/JNK) and p38. TGF-RI binds to one of its receptors and triggers Smad2/3-induced intracellular signaling.[15,21] They control integrins, connective tissue growth factors, metalloproteinases,

and plasminogen activator inhibitor-2 together with Smad4. In addition to enhancing these effects via stimulation of TGF-/MAPK/Smad signaling, angiotensin II directly activates JNK and p38, triggers the production of monocyte chemoattractant-1 protein, and stimulates the release of sST2.[12]

Angiotensin II also boosts the interleukin (IL)-33/sST2 pathway and reduces the cardioprotective effects of IL-33/ST2-ligand (ST2L).[13] Figure 2 summarizes ACEI-induced inhibition of the TGF-/MAPK/Smad signaling pathway to slow the evolution of RHD. Activation of MAPK and NF-B downstream through MyD88 and TNF receptor-associated factor occurs secondary to IL-33/sST2 stimulation. Inhibition of ACE via inhibition of TGF-/MAPK/Smad signaling during RHD progression increases IL-33/ST2L activity, which increases angiotensin II production and produces a cardioprotective effect.[15,20] In contrast to angiotensin receptor blockers, ACEIs not only inhibit the converting enzyme that produces angiotensin II but also potentiates the synergistic effects of bradykinin for cardio-protection and fibrosis attenuation by directly reducing IL-33 binding to sST2. Reduced angiotensin II generation lowers MAPK activity, TGF-activation, binding of Smad2/3 and Smad4, and causes direct inhibition of IL-33 binding to sST2 as its decoy receptor and minimizes cardiac fibrosis because RHD is considered an inflammatory condition.[12]

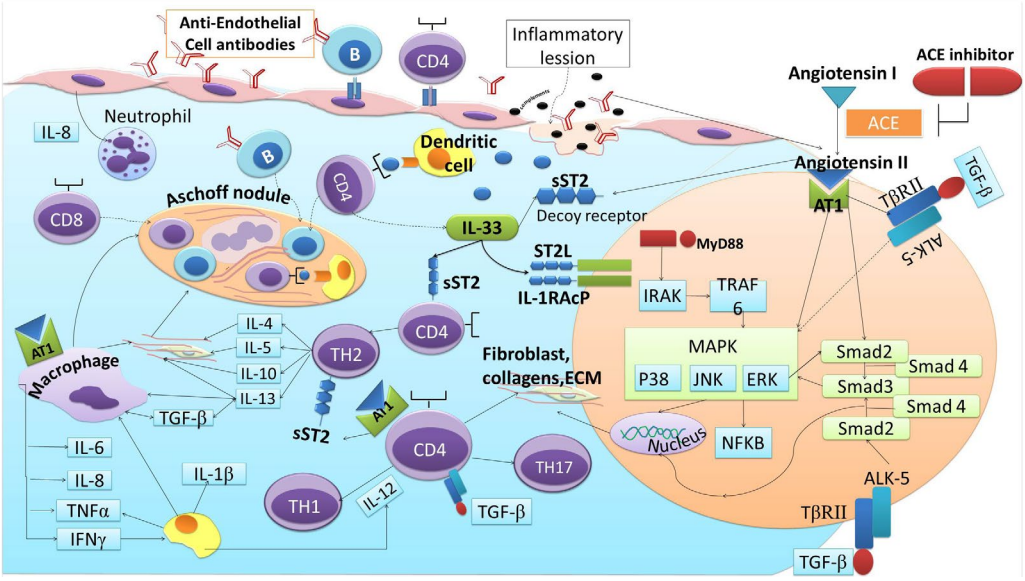


**Figure 2.** ACEI and ST2 involvement in cardiac fibrosis observed in RHD

The second chapter of the study describes the role of ACEIs in reducing fibrosis as the primary strategy to break the vicious cycle in RHD, which aids with reducing inflammation, fibrosis, and MV calcification and additionally highlights the clinical significance of ACEIs in treatment of RHD. ACEI may serve as a promising novel non-interventional therapeutic option to slow advancement of fibrosis in RMS.[14,16] Figure 3 illustrates the pathophysiological mechanism through which ACEIs slow RHD onset.

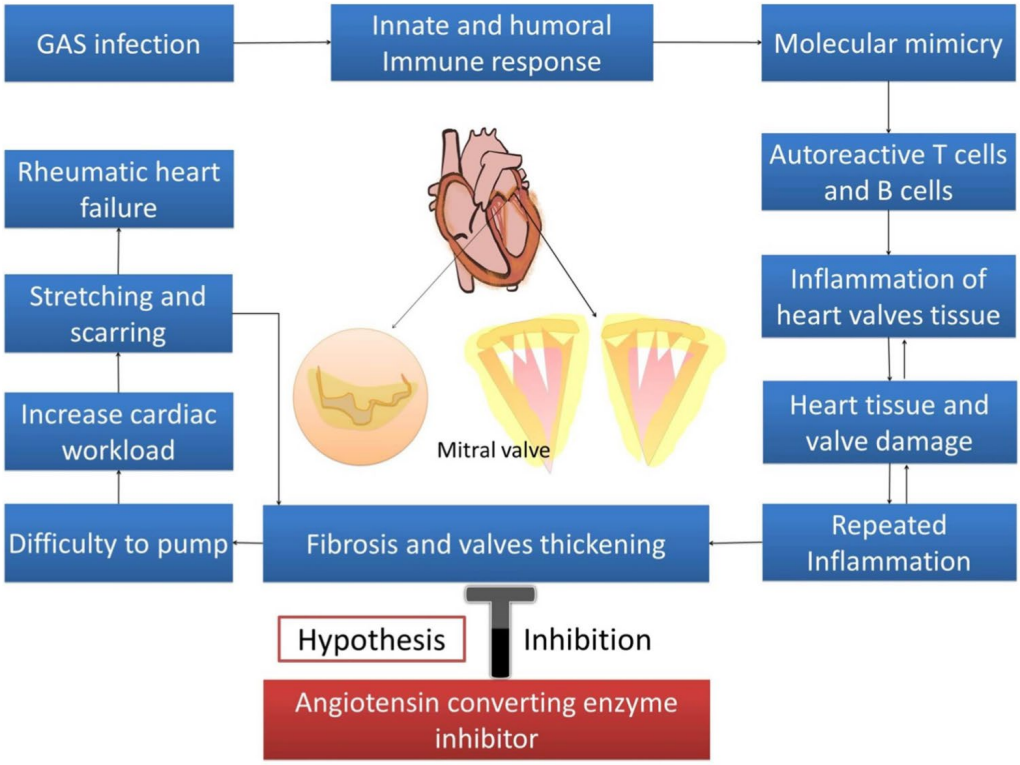


**Figure 3.** Role of ACEIs in reducing RHD progression

## Cost-effective therapeutic interventions for rheumatic mitral stenosis

Chapter 3 focuses primarily on the interventional management of RMS, particularly in low- to middle-income countries such as Indonesia. No national database has tracked the prevalence of RHD in Indonesia. Per World Health Organization (WHO) estimates (2015), RHD affected 1.18 million patients in Indonesia, which was ranked fourth among countries with the largest estimated numbers of RHD cases globally. Interventional therapy is deemed appropriate

for patients with RMS, who have clinically severe stenosis (MVA <1.5 $cm^2$). MV surgery is considered in patients with contraindications for PBMV or in those with a history of failed PBMV.[22] Reduced right ventricular (RV) function, the most common complication of MV surgery, affects the postoperative course of MV surgery. Many studies have reported an association between reduced RV function following MV surgery and poor long-term outcomes.[23–26]

PBMV is not recommended for patients with RMS and concomitant severe aortic valve disease, tricuspid stenosis and regurgitation that require surgery, in those with MVA ≥1.5 $cm^2$, LA thrombus, concomitant more-than-mild MR, severe or bi-commissural calcification, and absence of commissural fusion. In addition to publication of the European Society of Cardiology guideline for valvular disease (2021),[22] the American Heart Association guideline (2020) recommends surgical intervention for RMS in patients with New York Heart Association (NYHA) classes III/IV, with severe calcification or a history of unsuccessful PBMV.[27]

In addition to PBMV, MV surgery and concomitant LA reduction may be performed in patients with thrombosis. Owing to the structural changes associated with advanced RMS, this procedure may also be performed in patients with persistent atrial fibrillation. However, PBMV is performed using an antegrade percutaneous transseptal approach and the Inoue balloon technique under echocardiographic guidance; therefore, it is less invasive. Although MV repair is recommended whenever possible, in Taiwan, it is frequently performed in patients with RMS, who require surgical intervention. Usually, RMS lesions are more severe than those associated with a non-rheumatic etiology, and repair is more challenging because these lesions usually show greater calcification than that observed in degenerative lesions. MV repair necessarily involves commissurotomy, valvular debridement, ring annuloplasty, replacement of artificial chordae, and release of the subvalvular apparatus.[27]

At the National Cardiovascular Center in Harapan Kita, Jakarta, Indonesia, MV surgery is frequently used for surgical intervention in cases of RMS, and TEE is typically performed to exclude thrombosis or other contraindications to PBMV before considering patient eligibility for surgery. MV surgery is defined as either MV repair or MV replacement. Owing to its superior image quality compared with

conventional TTE, TEE provides a clearer view of certain structures, including the LA appendage, pulmonary veins, and mitral regurgitant jets in patients with a prosthetic MV.[28] The Wilkins' score is an echocardiographic grading system used to accurately determine the indications for surgical intervention in patients with RMS; patients with scores <8 are considered good candidates for PBMV. Surgical therapy is performed in patients with scores ≥8, particularly in those with more-than-moderate MR, except in patients with serious comorbidities. In Chapter 3, we compared the prognosis of patients with RMS undergoing PBMV with that of patients undergoing MV surgery and observed that PBMV was not inferior to MV surgery with regard to survival outcomes (mortality rate: 1.8% [6 of 329] patients who underwent PBMV, median follow-up 24 months vs. 3.5% [5 of 142] patients who underwent MV surgery, median follow-up 27 months).[29] Acute decompensated heart failure was the most common complication that necessitated rehospitalization in both groups, and rehospitalization rates did not significantly differ between patients who underwent PBMV and MV surgery. PBMV is recommended as first-line interventional therapy for patients with RMS in the absence of contraindications, despite a shorter event-free interval.

Compared with the MV surgery group, the event-free interval was 5 months shorter in the PBMV group. Although the sustained event-free duration was significantly better in the MV surgery group than in the PBMV group, the mortality rate in both groups were quite similar (3.5% in MV surgery vs 1.8% in PBMV). The difference in event-free interval might be driven by higher rehospitalization rates in the PBMV group (16%) compared to MV surgery group (9%). The possible causes of the difference in rehospitalization rates between PBMV and MVS were the lack of regular follow-up for PBMV patients. MVS patients were required to have follow-up appointments at our cardiac rehabilitation center at the National Cardiovascular Center Harapan Kita in Jakarta after the surgery, while PBMV patients were allowed to return to the referring hospital in their region for routine check-ups. Cardiac rehabilitation facilities in the regions are still limited due to Indonesia being an archipelago, and not all areas have comprehensive facilities. We suggested a solution for PBMV patients to be treated for a longer duration at the National Cardiovascular Center Harapan Kita for optimal care.

A Tanzanian study that investigated the variables associated with early surgical mortality in patients with RHD[30] reported that in-hospital mortality was greater than that previously reported. The risk of early mortality was higher in patients who underwent double-valve replacement than in those who underwent single-valve replacement for RHD, which emphasizes the importance of superior technical abilities and meticulous postoperative care. In most developing countries, patients invariably present during the late stages of the disease with severe symptoms; therefore, careful patient selection and correct surgical approach are extremely important.[31]

Considering the long event-free interval and high survival rate associated with PBMV (which is comparable with that of MV surgery), patients with RMS tend to favor PBMV, particularly in low- to middle-income nations, and expansion of PBMV capabilities focused on expert centers is encouraged. Expertise in PBMV should be improved and consolidated at local level.[32]

## Rehabilitative management after surgical intervention in patients with rheumatic mitral stenosis

Chapter 4 describes cardiac rehabilitation, which constitutes the post-intervention phase. Post-MV surgery cardiac rehabilitation in patients with RMS is an essential component of a comprehensive therapeutic strategy and does not involve only focused cardiac exercise but includes three primary phases.[33] Phases I and II are performed at a cardiac center or hospital; however, phase III may be completed at home. A multidisciplinary team is involved in phase I cardiac rehabilitation for health promotion, particularly post heart surgery. This phase includes post-MV surgery nutritional management, psychological support, and measures for progressive mobility improvement. Phase II, which aims to improve a patient's functional ability and quality of life is a transitional stage to acclimatize patients to the home environment with unsupervised exercise, which is prescribed during cardiac rehabilitation phase III.[33,34]

Cardiac rehabilitation evaluation in low- to middle-income nations involves assessment of patients' exercise capability to formulate an individualized exercise program. The 6-min walk test (6MWT) is used in preference to cardiopulmonary exercise testing (CPET) to evaluate post-MV surgery exercise

ability and reflects patients' functional capacity.[35] Although CPET with oxygen consumption ($VO_2$) measurement is the gold standard for evaluation of aerobic capacity, the Cahalin formula can be used to estimate VO2 in low- to middle-income countries based on results of the 6-min walking distance (6MWD).[36,37]

Early outcomes of phase II cardiac rehabilitation following MV surgery were comparable with those in patients who underwent open heart surgery (coronary artery bypass grafting).[38] At the Harapan Kita Cardiac Center in Jakarta, early cardiac phase II rehabilitation includes a minimum of 12 sessions and commences 2 weeks following MV surgery. The 6MWT is performed before and after cardiac rehabilitation. Patients' exercise capacity showed remarkable improvement after early phase II cardiac rehabilitation following MV surgery.[39]

Rheumatic heart failure or cardiac structural changes may occur in patients with RMS.[2] Despite these challenges, the post-MV surgery exercise performance showed significant improvement in patients with RMS. Physiological adaptation to meet high exercise-induced demand occurs in response to aerobic exercise and is manifested as an increase in oxygen absorption and delivery, followed by an improvement in cardiopulmonary function. Exercise increases cardiac output but maintains pulmonary resistance; however, patients with RMS showed a post-MV surgery decline in pulmonary arterial pressure and pulmonary wedge pressure. Phases I, II, and III of cardiac rehabilitation are strongly recommended, following successful MV surgery or other interventional therapy in patients with RMS.[39]

## Development of cost-effective non-interventional strategies for management of rheumatic mitral stenosis focused on valve fibrosis attenuation in low- to middle-income countries

Chapter 5 outlines the therapeutic options for valve fibrosis in patients with RMS.[40] Economic and social issues are typical concerns in low- to middle-income nations and have negative effects on healthcare access and quality.[41] All patients with RMS may not be diagnosed and may not be referred to a hospital with availability of interventional skills because of disparities between urban-rural settings and differences across geographic regions, which is also observed in Indonesia. Late referrals are attributable to lack of RHD

screening facilities owing to limited health infrastructure and access, patients' lack of understanding of RHD, and financial considerations.[42] Even patients diagnosed with RHD are occasionally reluctant to get referrals owing to the high expenditures associated with travel and lodging. Notably, patients with RMS who are referred already have significant disease and need interventional therapy, despite the availability of present RMS medications, which effectively relieve symptoms but do not delay the course of RHD.

Research is still underway to investigate administration of ACEI as an anti-fibrosis drug; this novel non-interventional therapy to reduce valve fibrosis in RMS may be beneficial in low- to middle-income countries. In Chapter 2, we described the possible role of ACEI in breaking the vicious cycle of inflammation and fibrosis that develops with RHD progression. In Chapter 5, we proposed a randomized controlled trial as a novel research strategy to confirm the possible advantages and disadvantages of ACEI administration in patients with RMS.[40]

ACEI-induced hypotension and fixed obstruction in the calcified stenosis, which may further reduce cardiac output, are causes of concern associated with ACEI use in patients with RMS. Chockalingam *et al.* observed that enalapril (an ACEI, maximum dose 10 mg twice daily) did not cause hypotension in symptomatic chronic RMS in patients with NYHA functional class III or IV, and patients who received enalapril showed significant improvements in the NYHA class, Borg Dyspnea Index, and 6MWD scores.[32]

We developed a research protocol to determine the antifibrotic effects of ACEI[40] and designed an RCT in which patients received ramipril (5 mg) for at least 3 months preoperatively. Patients with blood pressure readings <100/60 mmHg were excluded. Patients' symptoms, vital signs, and evidence of disease progression were monitored while patients used ramipril before the MV replacement, and ramipril administration (5 mg) was discontinued 5 days preoperatively. Patients were administered an initial dose of ramipril (2.5 mg) for one week to observe adaptation and development of any adverse effects, to monitor drug safety.

After MV replacement, the MV was stored for analysis of ST2 expression. The MV and papillary muscle tissues were extracted intraoperatively and preserved in a sterile container containing 10% formalin. Immunohistochemical analysis

was performed to confirm ST2 receptor expression in the valve and papillary muscles. Plasma blood samples were obtained a day before MV replacement and before ramipril or placebo administration to determine circulating sST2 levels. In this study, we investigated the pre- and post-intervention effects of ramipril (5 mg) with placebo on N-terminal proB-type natriuretic peptide concentration, echocardiographic strain parameters, clinical outcomes, plasma ST2 levels, and ST2 expression in MV tissue.

We hypothesized that ramipril (5 mg) would reduce fibrosis and inflammation of the MV and also the levels of circulating sST2, which serves as an IL-33 decoy receptor. The adverse effects of ramipril (5 mg) were also recorded. Based on safety data from previous studies, we anticipated that ramipril therapy initiated at a dose of 2.5 mg would not produce any observable adverse effects. A breakthrough in the non-interventional treatment of RMS using ramipril (5 mg) may minimize heart valve and tissue fibrosis and improve patient outcomes. This treatment will particularly benefit patients from low- and middle-income nations.

This study is currently underway. In our opinion, many patients fear cardiac surgery and prefer oral treatment and are often unwilling to participate in trials owing to anxiety and fear of being subjected to experiments. Therefore, patient recruitment for this study was difficult. Furthermore, based on the thoracic surgeon's direct evaluation of the patient's heart valves intraoperatively, most patients underwent MV repair and not replacement. Therefore, an adequate number of MV samples were unavailable.

## Role of penicillin for secondary prophylaxis in rheumatic heart disease

Chapter 6 describes the role of new medications and possible improvements in non-interventional and interventional therapies for RMS, as well as rehabilitation programs to improve prognosis of patients with RMS. Moreover, we have discussed secondary preventive options for RHD in this chapter. Even patients with definitive diagnosis of RHD and those who have undergone PBMV or MV surgery are at risk of GAS re-infection.[43–45] RHD remains endemic in many developing nations, despite the use of penicillin for secondary prevention of

ARF and RHD over decades.[46,47] We performed a meta-analysis and systematic evaluation of observational data described in Chapter 6 to determine whether penicillin administration should be continued as a supplementary preventative measure against RHD in the future.[48–52] Although autoimmunity is implicated as a pathophysiological contributor to RHD, secondary prevention using penicillin is required to prevent further GAS re-infection to avoid triggering an autoimmune response.

Oral and parenteral penicillin remains the mainstay of therapy in patients with ARF and RHD.[29] Satisfactory adherence to penicillin treatment is the key to RHD prevention.[53] Studies have observed a strong correlation between penicillin adherence and the success of secondary prevention. ARF recurrence and RHD progression significantly increased in patients with poor compliance and inconsistent penicillin doses. A drug adherence rate of ≥80% of scheduled penicillin doses is recommended.[54] Poor adherence to secondary prophylaxis was significantly correlated with recurrent ARF and RHD in Indonesia.[41,55]

Good adherence to secondary prevention measures can delay the onset of ARF and RHD. Additionally, secondary prevention increases the cost-effectiveness of RHD management from a financial perspective. Dixit *et al.*[56] observed that compared with standard medical therapy, secondary prophylaxis was more effective and cost-effective in reducing the number of RHD cases per 1000 individuals. Effective coordination between primary interventions such as health education, secondary interventions such as antibiotic prophylaxis, and tertiary interventions such as cardiac rehabilitation is important.[57–59]

## Management of acute rheumatic fever and rheumatic heart disease in Indonesia

Poverty, low community health literacy, lack of awareness among health care professionals, lack of trained personnel, and weak health systems constitute important barriers to early diagnosis, continuum of care, comprehensive assessment of surgical intervention eligibility, and postoperative follow-up. Notably, the significant decline in the incidence of rheumatic fever even before the development of antibiotics was attributable to improved social conditions and better access to primary health care services.[60]

Robust primary health care systems are essential for effective management of ARF and RHD in Indonesia (Figure 4). Owing to its complexity, it is preferable not to approach RHD as a stand-alone program distinct from other health care services, and improved awareness among health policymakers is essential for effective RHD management.[61] Government cooperation is necessary to develop a nationwide program in association with the Indonesian Pediatrics Society (Ikatan Dokter Anak Indonesia). The nationwide program requires active cooperation from primary care and educational institutions to implement screening in the community. Cardiology referrals should be advised in symptomatic cases or in individuals with apparent physical indicators of disease.

However, currently, the RHD screening program is not widely available across Indonesia. Accurate diagnosis of RHD remains challenging because of the high cost of diagnostic technologies and the need for skilled staff.[3] However, the transformation has commenced in Indonesia. Following collaboration with the Indonesia Heart Foundation, we performed screening echocardiography in a large number of elementary school students in Natuna (the northernmost part of the Province of Riau Islands) and Jakarta and have planned such programs in future in Morotai, Sulawesi. We intend to perform more routine cardiac screenings across Indonesia.

Although theoretically possible, implementation of primary prevention is challenging because it requires accurate identification of the GAS sore throat and administration of penicillin therapy. Up to 33% of patients who develop rheumatic fever do not recall experiencing any pharyngitis symptoms. Moreover, symptoms of pharyngitis are absent in up to 58% of infected patients. These facts serve as potential obstacles to the effectiveness of primary prevention of rheumatic fever with the sole use of antibiotic therapy for GAS pharyngitis. Therefore, additional primary prevention efforts should focus on health education regarding the risk of sore throat-induced ARF and improved awareness regarding identification of GAS infection-induced sore throat.[60]

Recurrent ARF episodes result in advanced RHD; therefore, secondary prevention should focus on antibiotic prophylaxis to avoid these episodes. In contrast to daily oral medication, 3–4 weekly intramuscular injections of

benzathine penicillin G are recommended for patients after an episode of ARF to achieve a balance between medication efficacy and patient compliance.[60]

Regular prophylactic penicillin therapy and patient monitoring using an RHD registry are important to ensure adequate adherence to RHD management. Disease prevalence can be determined by integration of regional RHD information into national databases. The patient's family should actively participate in care and be appropriately informed regarding the illness because consistent therapy is important. Similar to the pattern used in tuberculosis management, a drug supervisor (Pengawas Minum Obat) should be available to monitor medicine administration in each patient. Comprehensive community education and primary preventive measures should be emphasized in regions that show high RHD prevalence. Surveillance techniques and database completeness should be enhanced as sources of monitoring and data to aid with policy making. Screening tools and a sustainable antibiotic supply chain should be easily available to primary health care professionals (*pusat kesehatan masyarakat* [Puskesmas]) to assist physicians in early management of this disease.

The following factors should be considered before screening: the diagnostic approach, devices to be used, personnel who will perform the screening, the target population, and budget considerations. Reliable and inexpensive RHD screening assays should be available.

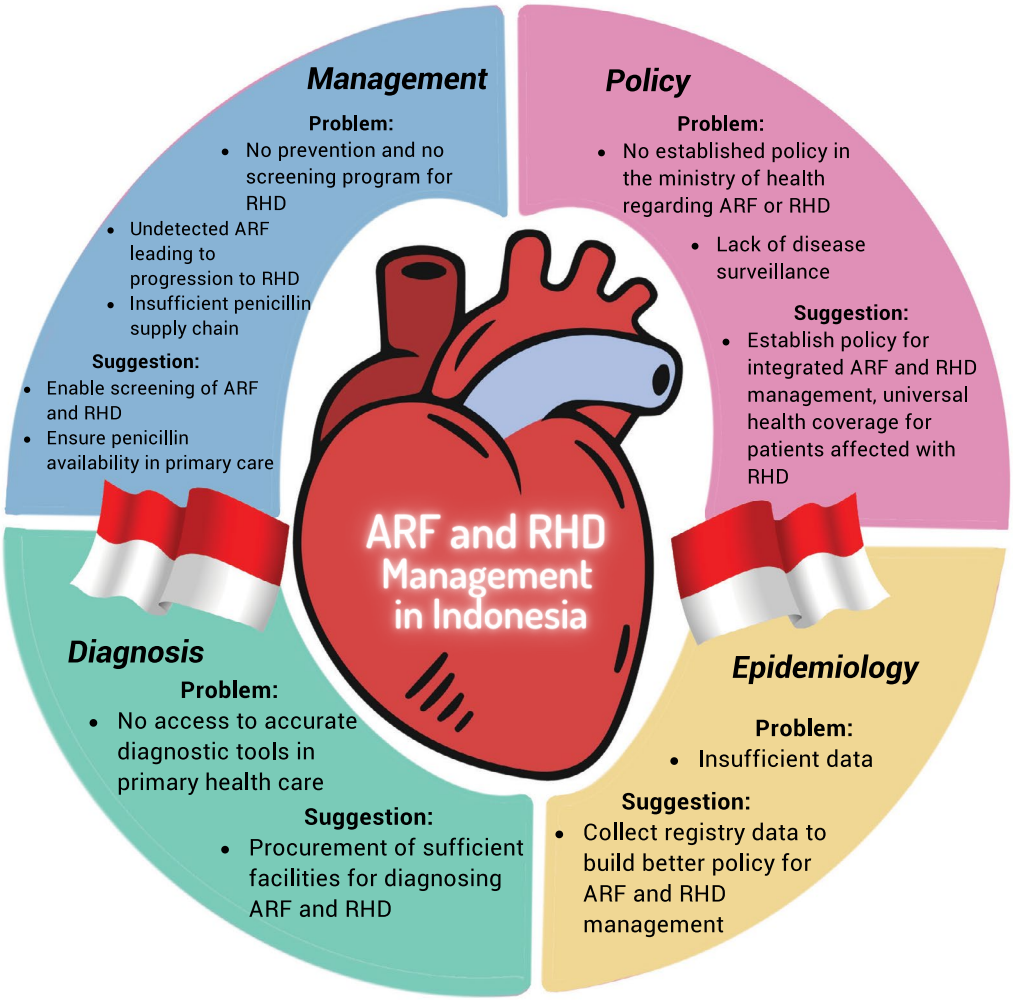


**Figure 4.** Central illustration showing ARF and RHD management in Indonesia. Some issues associated with RHD management need to be resolved through a holistic approach that involves building a systematic registry and database, establishing policies to manage RHD cases, creating a sustainable supply chain, and provisioning appropriate screening tools in primary care.

ARF: acute rheumatic fever, RHD: rheumatic heart disease


**Figure 5.** National Cardiovascular Center, Harapan Kita

The National Cardiovascular Center in Harapan Kita, Jakarta is a referral hospital and treats many patients across Indonesia. Treatment options include counseling, cardiovascular rehabilitation, antibiotic administration, and surgery. However, effective collaboration with primary health care facilities is essential for screening purposes and treatment of new cases. We at the aforementioned hospital intend to provide training in echocardiography and laboratory evaluation to equip general practitioners with the expertise required for early identification of ARF or RHD in their local communities. An effective network that can reduce referral red tape is essential to accommodate a large number of patients.

Basic prevention is a direct approach that is easy to implement and should be emphasized. Population education regarding ARF and RHD is important for effective RHD management. Puskesmas, which serve as primary health care community clinics located across Indonesia, integrated health programs (*pos pelayanan terpadu* [Posyandu]), which provide immunization services for children, and *pos binaan terpadu* [Posbindu]), which provide services for patients with non-communicable diseases, and "little doctors" (*Dokter Kecil*,

students appointed as peer health educators in schools), all represent channels that expand the reach of health care services across wide geographic areas of Indonesia (Figure 6).

The Puskesmas serves as the first point of contact with the health care system and caters to a wide range of patients; therefore, this local health facility is best suited to provide information regarding ARF and RHD. Posyandu and Posbindu, integrated health programs form useful components of the Puskesmas where mothers and elderly patients can obtain education regarding RHD (Figure 7). Our model includes "little doctors," who are trained to create health awareness in schools. Cadres that function across the Posyandu and Posbindu and "little doctors" all aid with early diagnosis of RHD in suspected cases. A successful referral system relies on thorough understanding of RHD, awareness of any indications or symptoms, and report preparation. The general practitioner who receives the report is obligated to monitor patients and screen them based on history taking and physical examination. Patients with a high index of clinical suspicion for RHD should be referred to secondary hospitals for cardiology evaluation using electrocardiography, chest radiography, echocardiography, and various laboratory investigations. Whether the patient requires referral to a higher level care for ongoing management or referral back to the Puskesmas is at the cardiologist's discretion, depending on the severity of the patient's illness at the time of consultation. Even those patients who are transferred to a referral hospital and complete treatment are eventually referred back to the Puskesmas for ongoing secondary or tertiary prevention to avoid recurrent ARF or RHD. Every step of the process should be carefully monitored and documented using an electronic medical records system to create a database and ensure effective follow-up.

Soesanto and Suastika were of the opinion that the program can only be successfully implemented through team work and strategic planning with collaboration between physicians across the country.[3] We concur with the aforementioned authors' views that successful RHD management programs require sincere effort and collaboration between various interrelated components of the health care delivery system, such as health care providers, health care facilities, patients and their families, the government, financial agencies, and the health care system.

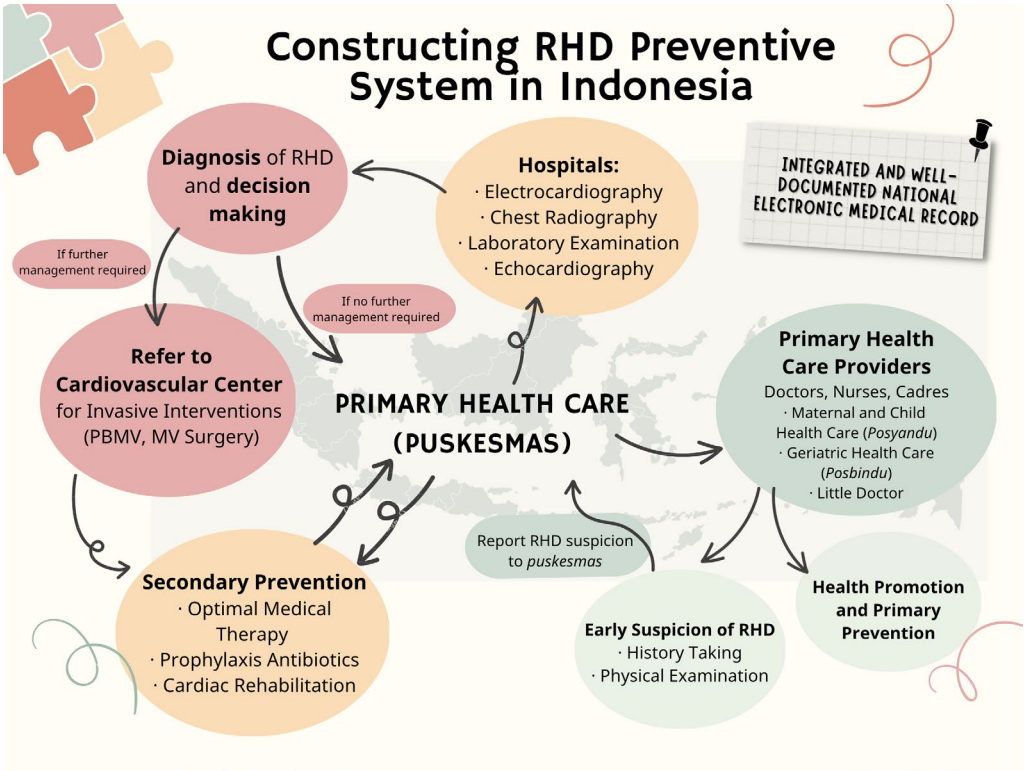


**Figure 6.** Diagrammatic representation of collaboration between primary health care centers (Puskesmas) and hospitals to prevent worsening rheumatic heart disease in Indonesia. Challenges to RHD management include lack of satisfactory knowledge regarding accurate history taking and physical examination for RHD screening among medical personnel, who require specialized training to increase awareness of RHD.

MV: mitral valve, PBMV: percutaneous balloon mitral valvuloplasty, RHD: rheumatic heart disease


**Figure 7**. Puskesmas, Posyandu, and Posbindu in the community serve as primary health care services in Indonesia. It is expected that the community can obtain affordable and easily accessible quality health services through this model.

***The topmost photograph*** shows a Puskesmas building in Yogyakarta. Basic services delivered through Puskesmas include health promotion and environmental health services, maternal, child, and family planning health services, and disease prevention and control services.

*The lower left photograph* shows activity at a Posbindu, where health care providers perform routine medical evaluation of urban residents or villagers, using resources owned by the local community. This photograph shows the home garage of the Chief of Village in Klaten.

*The lower right photograph* shows a Posyandu. Healthcare providers perform monthly health assessments of infants, toddlers, and children at the villagers' or city residents' homes. The photograph shows growth status assessment of a toddler in a Posyandu in Jakarta.

## Concluding remarks

All aspects of RHD, particularly RMS, should be thoroughly addressed, such as primary and secondary prevention, non-interventional care, interventional therapies, and rehabilitation. RMS is the most common valvular anomaly observed in RHD. Each aspect is useful and important. With regard to patient survival, effectiveness of PBMV was similar to that of MV surgery. Penicillin is preferred for secondary prevention of RHD, and cardiac rehabilitation significantly affects patients' functional gains. Future non-interventional treatments that attenuate cardiac valve and tissue fibrosis, such as ACEI administration and ramipril administered at a 5 mg dose (as recommended by the currently ongoing trial), may shorten the course of RHD and improve outcomes in patients with RMS. Numerous mechanisms underlie the role of ACEIs as antifibrotic agents to break the inflammatory domino effect in RHD, with consequent improvement in heart valve health and cardiac function. RHD remains ignored in Indonesia, and greater awareness regarding the aforementioned concerns is necessary. Appropriate patient management, comprehensive patient education, efficient government, health care provider, and health system coordination can reduce morbidity rates and minimize treatment costs and improve patient outcomes.

It may be necessary to integrate RHD control strategies with primary care services as an essential component of an all-encompassing national policy in areas with high RHD prevalence, such as Indonesia. Government initiative is necessary to ensure that the active pharmaceutical component is procured and penicillin is manufactured locally and supplied through efficient supply

chains to meet local demands. Medications may not be easily available across the country; therefore, ongoing advocacy and international cooperation with organizations such as the WHO will be crucial. ARF and RHD are not considered communicable disorders in many countries. Therefore, it may be difficult to develop a cohesive strategy that is applicable to diverse populations. Health policymakers should be aware of public health programs that reduce the risk of RHD and also the disease prevalence, geographical differences, and economic effects.

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# Appendix

## NEDERLANDSE SAMENVATTING

Reumatische Hartziekte (RHD) blijft een wereldwijde gezondheidslast. In 2017 werden wereldwijd ongeveer 38-40,8 miljoen gevallen van RHD geregistreerd. Er is een aanzienlijk verschil in prevalentie tussen endemische en niet-endemische regio's. De prevalentie van RHD in niet-endemische regio's is 3,4 gevallen per 100.000, terwijl endemische regio's meer dan 1.000 gevallen per 100.000 hebben. RHD beïnvloedt de vroegtijdige kindersterfte met een verhouding van 0,15/100.000 kinderen en een jaarlijks sterftecijfer van 1,5%. Hogere sterftecijfers zijn ook gemeld, waarbij Ethiopië en Pakistan percentages van 6-12% bereiken.

In Indonesië zijn er nog steeds geen uitgebreide nationale gegevens over de prevalentie en incidentie van RHD. In 1995 werd de prevalentie van RHD geschat op 0,3-0,8% bij kinderen van 5-15 jaar. Lokale rapporten zijn alleen beschikbaar uit Papua, Bandung en Jakarta. In Papua werd bij 83 van de 15.608 mijnwerkers RHD vastgesteld. Volgens het hartcentrum in Bandung was de prevalentie van RHD 2,3% in de regio Bandung (108 van de 4.682 patiënten). Het Nationaal Cardiovasculair Centrum Harapan Kita-ziekenhuis Jakarta registreerde 40,5% RHD-gevallen uit 7.112 klepziekten tijdens de periode 2016-2019.

Reumatische hartziekte is een vergevorderde auto-immuunreactie van een slijmvliesinfectie veroorzaakt door de Streptococcus pyogenes bacterie (Groep A Streptokok [GAS], Strep A). Deze chronische aandoening wordt veroorzaakt door enkele of terugkerende episodes van acute reumatische koorts. B-cellen en T-cellen maken onderscheid tussen GAS-antigenen en eigen-antigenen op basis van aminozuursequenties en structurele verschillen. Het M-eiwit is een antigen van GAS-bacteriën die overeenkomsten vertoont met menselijke eiwitten, zoals de spiraalvormige helix-γ-structuur in klepeiwitten, cardiaal myosine en tropomyosine. Bacteriële antigenen lijken ook op DNA, koolhydraten en andere eiwitten. Het vermogen van T-cellen om antigenen te herkennen is verstoord bij RHD, waardoor er immunologische kruisreacties ontstaan waarbij T-cellen eigen-antigenen aanvallen. Dit kan gebeuren door infectie, vaccinatie en herhaalde auto-immuunreacties.

Op dit moment worden de diagnosecriteria en klinische manifestaties nog steeds gebaseerd op de Jones-criteria. Patiënten met 2 hoofd criteria of 1 hoofd + 2 aanvullende criteria worden beschouwd als acute reumatische koorts. Als er 2 hoofd criteria of 1 hoofd + 2 aanvullende criteria of 3 aanvullende criteria aanwezig zijn, wordt dit beschouwd als een terugkerende acute reumatische koorts. Belangrijke of hoofd criteria omvatten myocarditis, chorea, erythema marginatum, subcutane knobbeltjes en polyartritis bij laagrisicopopulaties of polyarthralgie bij matige en hoogrisicopopulaties. Aanvullende criteria omvatten koorts (>38,5°C), verhoogde bezinkingssnelheid van rode bloedcellen (>60 mm/uur) en/of CRP (>3 mg/dL), en een ECG dat AV-blok laat zien na correctie voor de leeftijd. Echocardiografie helpt bij de diagnose en het bepalen van de prognose, o.b.v. klepafwijkingen met regurgitatie, verdikking en specifieke andere vormen van klepziekten.

In ons eerste onderzoek (**Hoofdstuk 2**) hebben we aangetoond dat ACE-remmers zeer gunstig zijn bij het verminderen van fibrose door vermindering van ontsteking, fibrose en klepverkalking. ACE-remmers kunnen mogelijk een nieuwe behandel behandel mogelijkheid te geven voor reumatische hartziekte.

In **Hoofdstuk 3** bespreken we de niet-invasieve behandeling van reumatische hartziekte in landen met een laag tot midden inkomen, zoals Indonesië. Er is geen compleet register van gevallen van reumatische hartziekte in Indonesië, maar in 2015 rapporteerde de WHO 1,18 miljoen gevallen, waarmee het op de vierde plaats ter wereld stond. Invasievebehandeling van reumatische hartziekte is vereist als er sprake is van significante stenose van de mitralisklep, de aanwezigheid van een trombus in het linker atrium, gelijktijdige milde, matige of ernstige mitralisinsufficiëntie, commissurale verkalking, of een combinatie van tricuspidalisstenose en -insufficiëntie dat een operatie vereist. Overeenkomstig de ESC-richtlijnen is een operatie geïndiceerd voor patiënten met reumatische hartziekte en NYHA III/IV-hartfalen met ernstige verkalking van de mitralisklep of een voorgeschiedenis van een mislukte Percutane Ballon Mitralisklep Plastiek (PBMP). In het Nationaal Cardiovasculair Centrum Harapan Kita-ziekenhuis wordt vaak gekozen tijdnes een operatie voor het vervangen van de mitralisklep als therapeutische optie, en vaak wordt een transesofageale echocardiografie (TEE) uitgevoerd om een trombus of andere

contra-indicaties voor PBMP uit te sluiten vóór de operatie. Om de objectiviteit te waarborgen, wordt het Wilkins-score systeem gebruikt voor echocardiografie om de indicaties voor een operatie te bepalen. Als de score >8 is, ondergaat de patiënt een operatie, vooral als er sprake is van matige mitralisinsufficiëntie.

In het volgende gedeelte wordt de prognose na een PBMP vergeleken met het vervangen van de mitralisklep bij reumatische hartziekte besproken. Van degenen die PBMP ondergingen, overleed 1,8% binnen 24 maanden, terwijl 3,5% van degenen die een vervanging van de mitralisklep ondergingen overleden waren binnen 27 maanden. Het aantal heropnames verschilde niet tussen de twee groepen. PBMP is de eerste keuze voor patiënten met reumatische hartziekte zonder contra-indicaties, omdat het sneller verlichting biedt in vergelijking met het vervangen van de mitralisklep. Qua kosten is PBMP betaalbaarder en minder invasief, wat voordeliger is in landen met een laag tot midden inkomen.

Na de procedure is uitgebreide en holistische hartrevalidatie noodzakelijk om de kwaliteit van leven van de patiënt te herstellen. Revalidatieactiviteiten zijn niet beperkt tot specifieke oefeningen. Het proces is verdeeld in drie fasen. Fase I en II worden uitgevoerd in het behanedelend ziekenhuis, terwijl fase III door de patiënt zelfstandig thuis wordt voortgezet. Fase I omvat een multidisciplinaire benadering van gezondheidsbevordering, dieetmanagement, psychologische ondersteuning en geleidelijke mobilisatie. Fase II heeft tot doel de functionele capaciteit te verbeteren. Deze fase dient als overgang naar fase III, die thuis wordt uitgevoerd.

Aan de andere kant wordt het gebruik van ACE-remmers als antifibrotische behandeling op dit momentoverwogen om het fibrotische proces bij reumatische mitralisklepstenose aan te pakken als een nieuwe niet-invasieve behandelingsoptie. Het is aangetoond dat ACE-remmers de ontstekingscyclus die leidt tot fibrose van de klep, kunnen doorbreken. We hebben een protocol voor een gerandomiseerde studie ontwikkeld om de mogelijke voordelen van ACE-remmerbehandeling bij patiënten met reumatische hartziekte en de bijwerkingen ervan te evalueren. Gezien de hypotensieve effecten en de contra-indicatie van van ACE-remmers igv ernstig verkalkte kleppenop basis van eerdere onderzoeken, hebben we ervoor gekozen om de antifibrotische

effecten van Ramipril te onderzoeken, te beginnen met een dosis van 5 mg gedurende minstens 12 weken (3 maanden) vóór de operatie. We vermoeden dat Ramipril de ontsteking en fibrose in de mitralisklep vermindert door de circulerende sST2-niveaus te verlagen. Ramipril 5 mg kan een doorbraak betekenen in de behandeling van reumatische hartziekte, waardoor de resultaten voor patiënten verbeteren en het kosteneffectief is in landen met een laag tot midden inkomen.

Preventie van reumatische hartziekte omvat het gebruik van penicilline als primaire en secundaire preventie. We hebben een meta-analyse uitgevoerd naar penicilline bij het voorkomen van terugkerende acute reumatische koorts en reumatische hartziekte. De resultaten gaven aan dat orale en injecteerbare penicilline de belangrijkste therapie blijven bij gevallen van acute reumatische koorts en reumatische hartziekte om herhaling en verslechtering te voorkomen. Het naleven van deze behandeling speelt een cruciale rol bij het remmen van de ontwikkeling van reumatische hartziekte.

## Conclusie

Reumatische hartziekte, specifiek reumatische mitralisklep stenose, is de meest voorkomende klepafwijking die optreedt en moet worden aangepakt door primaire preventie, secundaire preventie, niet-invasieve behandeling, intervasieve therapieën en revalidatie. Elke onderdeel is waardevol en behulpzaam bij het bieden van vooruitgang in de behandeling van reumatische hartziekte. Percutane Ballon Mitralisklep Plastiek (PBMP) is even effectief als het vervangen van de mitralisklep wat betreft de overleving van de patiënt. Penicilline wordt nog steeds aanbevolen en is gunstig voor de secundaire preventie van reumatische hartziekte, terwijl cardiale revalidatie ook gunstig is voor het verbeteren van de functionele capaciteit van de patiënten. ACE-remmers hebben het potentieel als antifibrotische behandeling bij reumatische hartziekte door de ontstekingscyclus te remmen. Het verstrekken van onderwijs aangaande reumatische hartziekte via patiëntenonderwijs en effectieve samenwerking tussen de overheid, gezondheidsdiensten en gezondheidszorgsysteem kan de morbiditeit verminderen, de behandelingskosten verlagen en de kwaliteit van leven van patiënten met reumatische hartziekten verbeteren.

## SUMMARY IN ENGLISH

Rheumatic Heart Disease (RHD) continues to be a global health burden. In 2017, approximately 38-40.8 million cases of RHD were recorded worldwide. There is a significant difference in prevalence between endemic and non-endemic regions. The prevalence of RHD in non-endemic regions is 3.4 cases per 100,000, while endemic regions have more than 1,000 cases per 100,000. RHD affects premature infant mortality with a ratio of 0.15/100,000 children and an annual mortality rate of 1.5%. High mortality rates have also been reported, reaching 6-12% in Ethiopia and Pakistan.

In Indonesia, there is still no comprehensive national data on the prevalence and incidence of RHD. In 1995, the prevalence of RHD was estimated at 0.3-0.8% among children aged 5-15 years. Local reports are only available from Papua, Bandung, and Jakarta. Eighty-three out of 15,608 mine workers in Papua were found to have RHD. According to the cardiac center in Bandung, the prevalence of RHD was 2.3% (108 out of 4,682 patients). Meanwhile, the National Cardiovascular Center Harapan Kita Hospital handled 40.5% of RHD cases out of 7,112 valve diseases during the period of 2016-2019.

Rheumatic heart disease is an advanced autoimmune phase of mucosal infection caused by Streptococcus pyogenes bacteria (Group A Streptococcus, Strep A). This chronic condition is caused by single or recurrent episodes of acute rheumatic fever. B-cells and T-cells differentiate between GAS antigens and self-antigens through amino acid sequences and structural adjustments. The M protein is an antigenic structure of GAS bacteria that shares similarities with human proteins, such as the coiled helix-γ structure in valve proteins, cardiac myosin, and tropomyosin. Bacterial antigens also resemble DNA, carbohydrates, and other proteins. The ability of T-cells to recognize antigens is disrupted, leading to cross-reactive immunological reactions as T-cells attack self-antigens. This can occur through infection, vaccination, and repeated autoimmune reactions.

Currently, the diagnosis criteria and clinical manifestations still use the Jones criteria. Patients with 2 major criteria or 1 major + 2 minor criteria are considered to have acute rheumatic fever initially. If there are 2 major criteria or 1 major + 2 minor criteria or 3 minor criteria, it is considered a recurrent acute rheumatic fever. Major criteria include carditis, chorea, erythema marginatum, subcutaneous nodules, and polyarthritis in low-risk populations or polyarthralgia in moderate and high-risk populations. Minor criteria include fever (>38.5°C), elevated erythrocyte sedimentation rate (>60 mm/h), and/or CRP (>3 mg/dL), and EKG showing AV block after considering age variables. Echocardiography assists in diagnosis and determining prognosis, such as valve abnormalities like regurgitation, thickening, and specific shapes.

In our first study (Chapter 2), we demonstrated that ACE inhibitors are highly beneficial in reducing fibrosis by improving inflammation, fibrosis, and valve calcification. ACE inhibitors are expected to become a new treatment for the management of rheumatic heart disease.

In Chapter 3, we discuss the non-intervention management of rheumatic heart disease in low- to middle-income countries like Indonesia. Specifically, we do not have a registry of rheumatic heart disease cases in Indonesia, but in 2015, the WHO reported 1.18 million cases, ranking it fourth in the world. Interventional management for rheumatic heart disease is required if there is significant stenosis in the mitral valve with an area 1.5 $cm^2$, the presence of thrombus in the left atrium, concurrent mild, moderate, or severe mitral regurgitation, commissural calcification, commissural fusion, or combination tricuspid stenosis and regurgitation requiring surgery. In line with ESC guidelines, surgery is indicated for patients with rheumatic heart disease and NYHA III/IV heart failure with severe calcification or a history of failed PBMV. At the National Cardiovascular Center Harapan Kita Hospital, mitral valve replacement surgery is often chosen as a therapeutic option, and TEE is usually performed to rule out thrombus or other contraindications for PBMV prior to surgery. To ensure objectivity, the Wilkins scoring system is used for echocardiography to determine the indications for surgery. If the score is >8, the patient undergoes surgery, especially if there is moderate mitral regurgitation.

In the next section, the prognosis of PBMV compared to mitral valve replacement for rheumatic heart disease is discussed. Of those who underwent PBMV, 1.8% died within 24 months, while 3.5% of those who underwent mitral valve replacement died within 27 months. The occurrence of rehospitalization did not differ between the two groups, with acute decompensated heart failure being the leading cause. PBMV is the first choice for patients with rheumatic heart disease without contraindications because it provides faster relief compared to mitral valve replacement. In terms of cost, PBMV is more affordable and less invasive, which is more beneficial for patients with rheumatic heart disease in low- to middle-income countries.

Following the procedure, comprehensive and holistic cardiac rehabilitation is necessary to restore the patient's quality of life. Rehabilitation activities are not limited to specific exercises. The process is divided into three phases. Phases I and II are conducted in the cardiac hospital, while phase III is continued by the patient independently at home. Phase I involves a multidisciplinary approach to health promotion, dietary management, psychological support, and gradual mobilization. Phase II aims to improve functional capacity. This phase serves as a transition before phase III, which is carried out at home.

On the other hand, the use of ACE inhibitors as anti-fibrotic treatment is now being considered to address the fibrotic process in rheumatic mitral stenosis valve as a non-intervention management. It has been demonstrated that ACE inhibitors can break the inflammatory cycle that leads to fibrosis in the valve. We have developed a randomized control trial protocol to evaluate the potential benefits of ACE inhibitor administration in patients with rheumatic heart disease and its side effects. Considering the hypotensive effects and calcified stenosis contraindication of ACE inhibitors based on previous research, we chose to investigate the anti-fibrotic effects of Ramipril, starting with a dose of 5mg for at least 12 weeks (3 months) before surgery. Our suspicion is that Ramipril reduces inflammation and fibrosis in the mitral valve by lowering circulating sST2 levels. Ramipril 5mg could be a breakthrough in the management of rheumatic heart disease, improving patient outcomes and proving highly beneficial in low- to middle-income countries.

Prevention of rheumatic heart disease includes the use of penicillin as primary and secondary prevention. We conducted a meta-analysis to reinforce the notion that penicillin is still highly beneficial in preventing recurrent acute rheumatic fever and rheumatic heart disease. The results indicated that oral and injectable penicillin remain the mainstay therapy in cases of acute rheumatic fever and rheumatic heart disease to prevent recurrence and deterioration. Adherence to treatment plays a crucial role in the development of rheumatic heart disease, along with positive culture results and high ASO titers.

## Conclusion

Rheumatic Heart Disease, specifically rheumatic mitral stenosis, is the most common valvular disorder that occurs and should be comprehensively addressed through primary prevention, secondary prevention, non-intervention management, intervention management, and rehabilitation. Each approach is valuable and helpful in providing advancements in the management of rheumatic mitral stenosis. Percutaneous balloon mitral valvuloplasty (PBMV) is as effective as mitral valve replacement in terms of patient survival. Penicillin is still recommended and beneficial for the secondary prevention of rheumatic heart disease, while cardiac rehabilitation is also beneficial for improving patients' functional capacity. ACE inhibitors also have the potential as anti-fibrotic agents in rheumatic heart disease by inhibiting the inflammatory cycle. Providing education on rheumatic heart disease through patient management and effective collaboration among the government, healthcare services, and healthcare system can reduce morbidity, lower treatment costs, and improve the quality of life for patients.

## RESUME BAHASA INDONESIA

Penyakit Jantung Rematik masih menjadi beban kesehatan di dunia. Pada tahun 2017, sekitar 38-40.8 juta kasus PJR tercatat di dunia. Terdapat perbedaan yang signifikan antara prevalensi di region endemik dan non endemik. Prevalensi PJR di region non-endemic adalah 3,4 kasus per 100.000, dan di sisi lain regio endemic memiliki kasus lebih dari 1.000 per 100.000. PJR bepengaruh pada kematian premature bayi dengan rasio 0,15/100.000 anak dengan angka kematian tahunan 1,5%. Angka kematian yang tinggi juga dilaporkan sampai 6-12% di Ethiopia dan Pakistan.

Di Indonesia, belum ada data nasional yang terintegrasi dan lengkap mengenai prevalensi dan insidens PJR. Tahun 1995, prevalensi PJR diperkirakan 0,3-0,8% pada anak dengan usia 5-15 tahun. Pelaporan local hanya ada didapatkan di Papua, Bandung dan Jakarta. Delapan puluh tiga orang dari 15.608 pekerja tambang di Papua menderita PJR. Menurut pusat pelayanan jantung di kota Bandung mencatat sebesar 2,3% (108 dari 4,682 pasien) didiagnosa PJR. Sementara itu, di RS Pusat Jantung dan Pembuluh Darah Harapan Kita menangani 40,5% kasus PJR dari 7112 penyakit katup selama tahun 2016-2019.

Penyakit jantung rematik merupakan fase autoimun lanjutan dari infeksi mukosa akibat bakteri *Streptococcus pyogenes* (Group A Streptococcus, Strep A). Kondisi kronik ini disebabkan oleh episode tunggal atau berulang dari demam rematik akut. Sel-B dan sel-T membedakan antigen GAS dan antigen diri sendiri melalui rangkaian asam amino dan penyesuaian struktur. Protein M adalah stuktur antigen dari bakteri GAS yang memiliki kesamaan dengan protein manusia seperti stuktur kumparan helix-γ pada protein katup, myosin jantung dan tropomiosin. Antigen bakteri juga mirip dengan DNA, karbohidrat dan protein lain. Kemampuan sel T dalam mengenali antigen akan terganggu sehingga dapat memicu reaksi silang imunologi karena sel-T menyerang diri sendiri. Hal ini bisa melalui infeksi, vaksinasi dan reaksi berulang autoimun.

Mekanisme pasti dari penyakit jantung rematik masih belum diketahui sampai saat ini, tapi beberapa ide dan hipotesis muncul untuk mengungkapkan patofisiologinya. Pada dasarnya, dicurigai penyebab nya akibat kemiripan imunologi atau reaksi silang antara antigen bakteri dan protein inang yang kecenderungannya seperti genetik pasien. Respon imun seluler dan humoral terpicu dari infeksi bakteri GAS di faring. Sel-B diproduksi setelah bakteri GAS direspon oleh sel penyaji antigen, makrofag dan sel dendritic. Selanjutnya mereka melepaskan TNF-α dan IFN-γ, mengaktifkan monosit dan meningkatkan makrofag, IL-8, IL-6 dan menarik neutrofil. Autoantibodi terdistribusi di aliran darah dan menempel pada endothelium katup jantung. Ekspresi VCAM-1 meningkat dan membuat sel-T datang ke subendotel. Korda tendinea akan memanjang serta membengkak, matriks ekstra seluler dengan antibodi antikolagen yang diselimuti agen proinflamasi. Dalam kondisi inflamasi, angiotensin II dan sST2 yang larut sebagai reseptor pengecoh juga meningkat. Mereka menstimulasi jalur fibrosis. Adhesi sel, proliferasi fibroblast, akumulasi ECM datang dari TGF-β yang memunculkan jaringan penghambat metalloproteinase (TIMP), penghambat matriks metalloproteinase (MMP) dan memicu faktor pertumbuhan jaringan. Jalur angiotensin II juga mempengaruhi IL-33/sST2. Penghambat ACE mengurangi produksi angiotensin II sehingga meningkatkan IL-33/sST2 dan efek proteksi jantung melalui penghambat sinyal TGF-β/MAPK/Smad pada perjalanan penyakit jantung rematik. Rangkaian kejadian ini membuat katup jantung, khususnya mitral menjadi rapuh.

Penentuan kriteria diagnosis dan manifestasi klinis saat ini masih memakai kriteria baru Jones. Pasien dengan 2 mayor atau 1 mayor + 2 minor dianggap demam rematik akut awal. Jika terdapat 2 mayor atau 1 mayor + 2 minor atau 3 minor merupakan kejadian berulang demam rematik akut. Kriteria mayor mencakup karditis, korea, eritema marginatum, nodul subkutan dan poliartritis jika pasien di populasi risiko rendah atau poliathralgia untuk populasi risiko sedang dan tinggi. Kriteria minor meliputi demam (>38,5$^{o}$C), laju sedimentasi eritrosit >60mm/h dan/atau CRP>3 mg/dL dan EKG menunjukkan AV blok setelah mempertimbangkan variable umur. Pada ekokardiografi membantu untuk diagnosa dan menentukan prognosis seperti kelainan katup seperti regurgitasi, penebalan dan bentuk tertentu.

Pada studi pertama (BAB 2) kami, menunjukkan bahwa penghambat ACE sangat bermanfaat dalam mengurangi fibrosis dengan cara memperbaiki inflamasi, fibrosis dan kalsifikasi katup. Diharapkan penghambat ACE bisa menjadi obat baru untuk penatalaksanaan penyakit jantung rematik.

Pada BAB 3, kami mendiskusikan mengenai penanganan non-intervensi dari penyakit jantung rematik di negara dengan pendapatan rendah-menengah seperti Indonesia. Secara khusus kami tidak mempunyai daftar registri penyakit jantung rematik di Indonesia, tetapi di tahun 2015, WHO mencatat terdapat 1,18 juta kasus dan menduduki posisi ke-4 di dunia. Penanganan intervensi untuk PJR jika terdapat stenosis signifikan pada katup mitral dengan area ≤1.5 cm2, muncul thrombus di atrium kiri, secara bersamaan juga terdapat mitral regurgitasi ringan, berat atau kalsifikasi bikomisura, adanya fusi kumisura, atau stenosis tricuspid kombinasi dan regurgitasi yang memerlukan operasi. Sejalan dengan ESC, operasi diperlukanbgai pasien PJR dengan gagal jantung klasifikasi NYHA III/IV dengan kalsifikasi berat atau riwayat gagal PBMV. Di RS Pusat Jantung Nasional Harapan Kita, operasi penggantian katup mitral sering menjadi pilihan terapi dan TEE biasanya dilakukan untuk menyingkirkan thrombus atau kontraindikasi lain untuk PBMV sebelum operasi. Agar objektif, penggunaan sistem penilaian The Wilkins untuk echokardiografi dilakukan dalam menentukan indikasi operasi. Jika nilainya >8, pasien akan menjalani operasi, terkhusus jika terdapat mitral regurgitasi sedang.

Di bagian selanjutnya, prognosis PJR yang menjalani PBMV dibandingkan dengan penggantian katup mitral. Sebanyak 1.8% yang menjalani PBMV meninggal dalam 24 bulan sedangkan 3.5% yang menjalani penggantian katup mitral, meninggal dalam 27 bulan. Kejadian rehospitalisasi tidak berbeda diantara keduanya dengan penyebab gagal jantung akut terdekompensasi. PBMV menjadi pilihan pertama pada pasien PJR tanpa kontraindikasi karena mengatasi lebih cepat dibandingkan penggantian katup mitral. Dari biaya, PBMV lebih terjangkau dan lebih tidak invasive yang lebih membantu dan menguntungkan pada pasien PJR di negara dengan pendapatan rendah-sedang.

Pasca tindakan, diperlukan rehabilitasi jantung secara komprehensif dan holistik untuk mengembalikan kualitas hidup pasien. Kegiatan rehabilitasi tidak terbatas pada olahraga tertentu. Prosesnya dibagi menjadi 3 fase. Fase I dan II dilakukan di rumah sakit jantung sementara fase 3 dilanjutkan pasien secara mandiri di rumah. Fase 1 melibatkan multidisiplin untuk promosi kesehatan, managemen diet, dukungan psikologis dan mobilisasi bertahap. Fase II bertujuan untuk meningkatkan kapasitas fungsional. Momen ini sebagai transisi sebelum fase III yang akan dilakukan di rumah.

Di sisi lain, pengobatan menggunakan penghambat ACE sebagai anti-fibrosis sekarang sedang dalam pertimbangan untuk mengatasi proses fibrosis katup pasien rematik metral stenosis sebagai tatalaksana non-intervensi. Sudah dipaparkan bahwa penghambat ACE dapat memutus siklus inflamasi yang membentuk fibrosis pada katup. Kami membuat protokol untuk uji kontrol teracak mengevaluasi potensi benefit dari pemberian penghambat ACE pada pasien PJR dan efek samping. Mempertimbangkan efek hipotensi dan stenosis terkalsifikasi dari penghambat ACE kontradiktif terhadap penelitian sebelumnya mengenai Enalapril (maksimal dosis 10mg, 2x sehari) tanpa menyebabkan hipotensi. Demi faktor keamanan, kami mengembangkan studi protocol dengan Ramipril 5mg setidaknya 12 minggu (3 bulan) sebelum operasi untuk menginvestigasi efek anti-fibrosis. Kecurigaan kami adalah Ramipril mengurangi inflamasi dan fibrosis di katup mitral dengan menurunkan sST2 yang bersikulasi. Ramipril 5mg dapat menjadi terobosan dalam proses tatalaksana PJR yang bisa memperbaiki keluaran pasien dan bisa sangat bermanfaat negara berpendapatan rendah-sedang.

Bentuk pencegahan PJR salah satunya dengan penggunaan penicillin sebagai prevensi primer dan sekunder. Kami melakukan meta-analisis untuk menguatkan bahwa penicillin masih sangat bermanfaat dalam mencegah kejadian berulang demam rematik akut dan mencegah PJR. Hasilnya, kami menemukan bahwa penisilin oral dan injeksi masih menjadi terapi utama pada kasus demam rematik akut dan PJR untuk mencegah kejadian berulang dan perburukan. Kepatuhan berobat sangat berpengaruh dalam perkembangan PJR, hasil kultur yang positif dan titer ASO yang tinggi.

## Kesimpulan

Penyakit Jantung Rematik, secara khusus rematik mitral stenosis adalah kelainan katup terbanyak yang terjadi dan harus bisa diatasi secara komprehensif dari prevensi primer, prevensi sekunder, penanganan non-intervensi, penanganan intervensi dan rehabilitasi. Setiap pendekatan akan sangat berharga dan membantu dalam memberikan perkembangan prnyakit rematik mitral stenosis. PBMV sama baiknya dengan pergantian katup mitral dalam kelangsungan hidup pasien. Penisilin masih direkomendasikan dan bermanfaat untuk prevensi sekunder dari PJR dimana rehabilitasi jantung juga bermanfaat untuk perbaikan kapasitas fungsional pasien. Penghambat ACE juga berpotensi sebagai anti-fibrosis pada PJR di masa depan dengan mekanismenya yang menghambat siklus inflamasi. Pemberian edukasi mengenai PJR melalui penanganan pasien dan kolaborasi efektif antara pemerintah, pelayanan kesehatan dan sistem kesehatan dapat menurunkan morbiditas, menurunkan biaya pengobatan dan meningkatkan kualitas hidup pasien.

## CONTRIBUTING AUTHORS


### Ade Meidian Ambari

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

### Pieter A. Doevendans

Department of Cardiology, University Medical Centre Utrecht, Utrecht, The Netherlands

Central Military Hospital, Netherlands Heart Institute, Utrecht, The Netherlands

### Maarten Jan Cramer

Department of Cardiology, University Medical Centre Utrecht, Utrecht, The Netherlands

### Budhi Setianto

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

### Anwar Santoso

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

**Basuni Radi**

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

**Bambang Dwiputra**

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

**Annemiek Wind**

Department of Cardiology, University Medical Centre Utrecht, Utrecht, The Netherlands

**Estu Rudiktyo**

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

**Amir Aziz Alkatiri**

Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, West Jakarta, Jakarta, Indonesia

### Arinto Bono Adji

Department of Thorax Cardio Vascular Surgery, Faculty of Medicine, National Cardiovascular Center Harapan Kita, University of Indonesia, Jakarta, Indonesia

### Eliana Susilowati

Research Assistant of Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

### Fadilla Tulrahmi

Research Assistant of Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

### Dean Arityanti

Research Assistant of Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

### Thomas Rikl

Research Assistant of Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

### Maria Patricia Inggriani

Research Assistant of Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, West Jakarta, Jakarta, Indonesia

## CURRICULUM VITAE

### Ade Meidian Ambari

National Cardiovascular Center Harapan Kita

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia

Jakarta, Indonesia

E-mail: ade.ambari@inaprevent.org

Ade Meidian Ambari was born in Banding Agung, South Sumatra on May 20th, 1977. He graduated from a public high school in Jakarta in 1995. He pursued his medical doctor from the Faculty of Medicine, Universitas Indonesia. After graduating in 2001, Ade was devoted to working in a remote area in West Lampung for three years. In 2007, Ade started his residency in cardiology at the National Cardiovascular Center Harapan Kita Hospital, Jakarta, Indonesia. Then, he continued to work as a cardiology staff at Harapan Kita until present. During his work, Ade developed a passion for cardiac prevention and rehabilitation, and decided to pursue training at the Faculty of Medicine, University of Utrecht. In 2017, he started his PhD on the topic of rheumatic heart disease under supervision of Prof. Dr. Pieter A. Doevendans, Dr. Martin Jan Cramer, Prof. Dr. Budhi Setianto, and Dr. Anwar Santoso. He was eager to study management of rheumatic heart disease especially in low-to-middle-income country. In addition to being a clinician, researcher, passionate teacher, and devoted father, Ade grew his leadership potential and served as the chairman of cardiac prevention and rehabilitation department, Indonesian Heart Association. Ade was appointed as the President elect of Indonesian Heart Association 2025-2028. Ade currently lives with his wife Andi Fatimah and his three children, 2 daughters and 1 son, Naurah, Arya, and Princessa. Living his motto of “Life is Good," he enjoys playing football and cycling during his spare time.

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# Management of Rheumatic Heart Disease in Low and Middle Income Countries Focus on Indonesia

Ade Meidian Ambari