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Indonesian Journal of Cardiology

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Volume 46, Issue II, 2025

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AUTHOR GUIDELINES

Indonesian Journal of Cardiology (IJC) is a peer-reviewed and open-access journal established by the Indonesian Heart Association (IHA)/*Perhimpunan Dokter Spesialis Kardiovaskular Indonesia* (PERKI) on the year 1979. This journal is published to meet the needs of physicians and other health professionals for scientific articles in the cardiovascular field. All articles (research, case report, review article, and others) should be original and have never been published in any magazine/journal. Prior to publication, every manuscript will be subjected to double-blind review by peer reviewers. We consider articles on all aspects of the cardiovascular system, including clinical, translational, epidemiological, and basic studies.

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Original Article

Dyslipidemia management among patients with high and very high cardiovascular risk in Indonesia: a multi-center registry

Sunanto Ng[1], Anwar Santoso[2], Renan Sukmawan[2], Erwinanto[3], Erika Adam[4], Dwita Desandri[2], Rita Zahara[2], Sony Wicaksono[5], Magma Purnawan Putra[6], Teuku Heriansyah[7], Badai Bhatara Tiksnadi[3], Yusra Pintaningrum[8]

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Abstract

Background: Indonesia, the world's largest archipelago, faces significant challenges in equitable healthcare delivery due to its geographical and infrastructural disparities. Atherosclerotic Cardiovascular Disease (ASCVD) remains the leading cause of mortality, with over 659,000 deaths recorded in 2019. Effective dyslipidemia management is crucial for preventing adverse ASCVD events. Unfortunately, the lack of implementation of an updated national lipid management registry might hinder an optimal strategy for the adverse events. This study evaluated dyslipidemia cholesterol management practices among high- and very high-risk patients across the country.

Methods: The study recruited 322 patients from eight centers across six provinces in Indonesia between May 2022 and March 2023. Patients were stratified based on the ASCVD risk and followed over three visits. Baseline clinical characteristics, lipid profiles, and treatment regimens were analyzed. Descriptive statistics summarized continuous and categorical variables, and low-density lipoprotein cholesterol (LDL-C) achievement was assessed.

Results: Of the 322 patients, 98.8% were very high-risk, with only 4.9% achieving <55 mg/dL and 21.2% achieving <70 mg/dL. Moderate-intensity statins were the most prescribed (51.2%), followed by high-intensity (36.6%). LDL-C reduction was most pronounced in private insurance patients, achieving a mean LDL-C of 69.8 mg/dL at the third visit compared to 98.9 mg/dL in National Health Insurance (*Jaminan Kesehatan Nasional*/JKN) participants. Missed visit rates increased over time, with 57.5% of patients missing the third visit, predominantly among JKN participants and low-income groups.

Conclusions: The majority of the population failed to achieve the recommended target of LDL-C levels. Dyslipidemia management in Indonesia remains suboptimal, with disparities driven by socioeconomic factors. Improved policies addressing medication availability, national lipid registry establishment, and equitable healthcare access are essential to enhance lipid management and reduce the burden of ASCVD in Indonesia.

(Indonesian J Cardiol, 2025;46;51-63)

Keywords: *Cholesterol, LDL-C, ASCVD, Indonesia.*

Introduction

Indonesia, the world's largest archipelago, consists of over 17,000 islands spreading across its vast territory with a population measuring up to 282 million people by mid-2024.[1] The geographical uniqueness and the country's still-developing infrastructure present a significant challenge in ensuring equitable healthcare access across the nation. Healthcare services, including specialized care for Atherosclerotic cardiovascular disease (ASCVD), remain largely centralized in urban centers in Java Island. The Central Bureau of Statistics reported that in 2015, Indonesia had more than 9,000 primary healthcare facilities. One-third of these hospitals are located within Java Island; meanwhile, eastern regions like Papua only have 200 hospitals covering the entire island.[2] Consequently, residents of remote and underdeveloped regions face considerable difficulties in accessing adequate healthcare facilities, which has a direct impact on the management of chronic diseases, including dyslipidemia and ASCVD.

ASCVD remains a leading cause of morbidity and mortality in Indonesia. The prevalence of ASCVD in Indonesia reveals a threefold increase from 0.5% in 2013 to 1.5% in 2018.[3-4] Despite the seemingly low prevalence, ASCVD remains the leading cause of death in Indonesia, with 659,000 deaths recorded in 2019 according to the Institute for Health Metrics and Evaluation, a significant increase compared to 20 years ago (292,000 deaths recorded).[5] Patients at high and very high ASCVD risk, as per the guideline, require optimal dyslipidemia management as part of their treatment strategy. Effective lipid management plays a pivotal role in preventing major adverse ASCVD events; however, the lack of a comprehensive national lipid registry in Indonesia hampers the monitoring and evaluation of cholesterol management practices across the country. Without such information, identifying gaps in care, assessing treatment adherence, and formulating evidence-based policies become increasingly challenging.

Further complicating the issue is the limited coverage of statin drugs under Indonesia's National Health Insurance (*Jaminan Kesehatan Nasional*/JKN), particularly in primary healthcare settings. High-intensity statins, which are recommended as first-line therapy for patients with high and very high cardiovascular risk,[6-7] are often under-prescribed or inconsistently available due to financial constraints and limited formulary access within the JKN framework. This limitation disproportionately affects patients in rural and underserved areas, where primary healthcare facilities serve as the first and gatekeepers for medical care.

Given these challenges, there is an urgent need to evaluate and address dyslipidemia management practices among patients with high and very-high ASCVD risk in Indonesia. This study aims to understand the current gaps in dyslipidemia management in Indonesia in patients with high and very high cardiovascular risk, and to explore the clinical and non-clinical factors that may be related to the gaps.

Methods

Study design and population

This was an observational, prospective cohort study enrolling patients with high and very high cardiovascular risk who were stratified according to the 2019 European Society Guidelines (ESC) guideline.[7] Patients were recruited from eight centers spread across six provinces in Indonesia. Centers in Java Island were from Jakarta (National Cardiovascular Center Harapan Kita, Pertamina Center Hospital); West Java (University of Indonesia Hospital, Dr. Hasan Sadikin General Hospital); and Banten (Siloam Hospital Lippo Village). Centers from other islands were from Aceh (Dr. Zainoel Abidin General Hospital), East Nusa Tenggara (Prof. Dr. W.Z. Johannes General Hospital), and West Nusa Tenggara (NTB Province General Hospital). The recruitment period lasted from May 2022 to March 2023.

Inclusion and exclusion criteria

Inclusion criteria were patients ≥18 years old and had low-density lipoprotein cholesterol (LDL-C) levels recorded within the last three months. Pregnant, breastfeeding patients, or patients currently involved in interventional research impacting LDL-C were excluded.

Data collection

Baseline characteristics data were obtained from the first outpatient visit through direct interview by study coordinators or research assistants from respective sites. Laboratory measurements were collected from electronic medical records. Follow-up data were obtained from two different outpatient visits, with a one-month interval from the first (baseline) to the second visit, and a three-month interval from the second to the third visit. An electronic data capture system with REDCap (project-redcap.org) was utilized for data entry from each center.

Statistical analysis

Continuous data with normal distribution were reported using mean and standard deviation; meanwhile, skewed continuous data were reported as median and interquartile range. Categorical data were reported as frequencies and percentages. Missing data were shown as frequencies.

Results

A total of 324 patients were screened, and two were ineligible for the study. This study finally enrolled 322 eligible patients, categorized into very high-risk (n = 318) and high-risk (n = 4) ASCVD groups. Patient recruitment flow during the study is shown in Figure 1. Overall baseline characteristics were presented according to ASCVD risk stratification in Table 1. A majority of the participants were male (77.6%). This study included a variety of Asian ethnicities, which were predominantly Malayan.

Payment for healthcare was primarily through the national health insurance or JKN (78.6%). A smaller portion used private insurance (6.8%) or paid out-of-pocket (9.3%). All very high-risk patients had a history of ASCVD. Average LDL-C levels in both groups were high, at 107.6 ± 45.1 mg/dL and 237 ± 37 mg/dL, respectively. Moderate-intensity statins were most prescribed (51.2%), while only 36.6% were on high-intensity statins.

Characteristics of the population with ASCVD were presented in Table 2. Coronary-related ASCVD was the most prevalent, found in 89.4% of the population. The mean age varied by group, with the coronary group having a mean age of 58.9 years, while the polyvascular group showed the highest mean age of 61.4 years. Hypertension and diabetes were the most prevalent comorbidities in the coronary group.

The population with ASCVD was mostly coronary-related, with male gender being more prevalent. The mean age varied by group, with the coronary group having a mean age of 58.9 years.

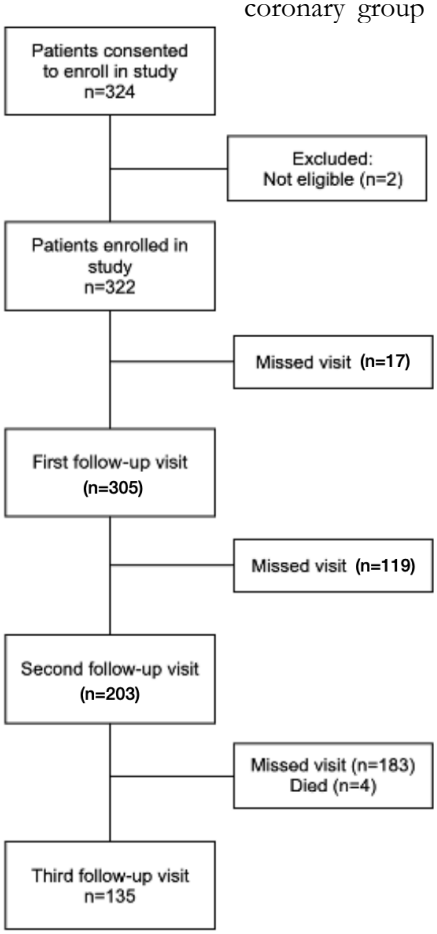

Figure 1. Recruitment and follow-up flowchart.

Table 1. Baseline characteristics according to risk stratification.

Characteristics	Overall (n = 322)	Cardiovascular risk	
		Very high-risk (n = 318)	High-risk (n = 4)
Male sex, n (%)	250 (77.6)	250 (78.6)	0 (0)
Age (years), mean ± SD	58.8 ± 10	58.7 ± 10	68.2 ± 8.3
Race, n (%)			
Proto-Malay	40 (12.4)	40 (12.5)	0 (0)
Deutro-Malay	128 (39.7)	128 (40.2)	0 (0)
Chinese	31 (9.6)	31 (9.7)	0 (0)
Weddoid	2 (0.6)	2 (0.6)	0 (0)
Others	88 (27.3)	86 (27)	2 (50)
Payment status, n (%)			
National health insurance (JKN)	253 (78.5)	251 (78.9)	2 (50)
Private insurance	22 (6.8)	22 (6.9)	0 (0)
Out-of-pocket	30 (9.3)	30 (9.4)	0 (0)
Estimated monthly income, n (%)			
>25 million IDR	21 (6.5)	21 (6.6)	0 (0)
5-25 million IDR	86 (26.7)	86 (26.7)	0 (0)
<5 million IDR	113 (35)	111 (34.9)	2 (50)
No income	49 (15.2)	49 (15.4)	0 (0)
Recruitment center, n (%)			
Java island	151 (46.9)	150 (47.1)	1 (25)
Other islands	171 (53.1)	168 (52.8)	3 (75)
Previous ASCVD, n (%)*	318 (98.7)	318 (100)	0 (0)
Acute coronary syndrome	221 (68.6)	221 (68.6)	0 (0)
Stable angina	108 (33.5)	108 (33.5)	0 (0)
Coronary revascularization	145 (45)	145 (45)	0 (0)
Stroke or transient ischemic attack	18 (55.9)	18 (56.6)	0 (0)
Peripheral arterial disease	1 (0.3)	1 (0.3)	0 (0)
Documented plaque from imaging	95 (29.5)	95 (29.8)	0 (0)
Hypertension, n (%)	183 (56.8)	179 (56.2)	4 (100)
Diabetes, n (%)	111 (34.4)	110 (34.6)	1 (25)

Characteristics	Overall (n = 322)	Cardiovascular risk	
		Very high-risk (n = 318)	High-risk (n = 4)
with target organ damage, n (%)	48 (14.9)	48 (15)	0 (0)
BMI (kg/m^2), mean ± SD	25 ± 3.7	25 ± 3.6	21.5 ± 1.7
Familial hypercholesterolemia, n (%)			
Definite	1 (0.3)	1 (0.3)	0 (0)
Probable	4 (1.2)	4 (1.2)	0 (0)
Possible	42 (13)	41 (12.8)	1 (25)
History of smoking, n (%)			
Active	29 (9)	29 (9.1)	0 (0)
Former	120 (37.2)	120 (37.7)	0 (0)
Never	152 (47.2)	149 (46.8)	3 (75)
Smoking duration (years), mean ± SD	32.9 ± 13.7	32.9 ± 13.7	N/A
Achieved recommended daily physical activity, n (%)$^+$	67 (20.8)	66 (20.7)	1 (25)
LDL-C (mg/dL), mean ± SD	108.4 ± 46.3	107.6 ± 45.1	237 ± 37
non-HDL (mg/dL), mean ± SD	137.8 ± 84.7	137.5 ± 23.5	214 ± 0
Total cholesterol (mg/dL), mean ± SD	176.7 ± 85.1	176.4 ± 34.1	256 ± 0
HDL (mg/dL), mean ± SD	40.3 ± 14.1	40.3 ± 11.6	42 ± 0
Triglyceride (mg/dL), mean ± SD	154 ± 105.6	136.2 ± 23.4	171 ± 46
Lp(a) (mg/dL), mean ± SD	7.65 ± 0.2	7.65 ± 0.2	N/A
ApoB (mg/dL), mean ± SD	54.5 ± 14.8	54.5 ± 14.8	N/A
Systolic BP (mmHg), mean ± SD	124 ± 19	124 ± 19	135 ± 5.7
Diastolic BP (mmHg), mean ± SD	75 ± 12	75 ± 11	84 ± 4.9
Statin intensity, n (%)			
High	118 (36.6)	118 (37.1)	0 (0)
Moderate	165 (51.2)	165 (51.8)	0 (0)
Low	4 (1.2)	4 (1.2)	0 (0)
No previous statin use, n (%)	19 (5.9)	17 (5.3)	2 (50)
Use of other LLTs, n (%)			
Ezetimibe	5 (1.5)	5 (1.5)	0 (0)
Fenofibrate	12 (3.7)	12 (3.7)	0 (0)

*Some patients may receive multiple diagnoses

+Recommended
ASCVD, Atherosclerotic Cardiovascular Disease; BMI, Body Mass Index; HDL, High-Density Lipoprotein; JKN, Jaminan Kesehatan Nasional (National Health Insurance); LDL-C, Low-Density Lipoprotein Cholesterol; LLT, Lipid-Lowering Therapy; Lp(a), Lipoprotein(a); ApoB, Apolipoprotein B.

Table 2. Baseline characteristics of patients with ASCVD.

Characteristics	ASCVD category*				
	Coronary (n = 288)	**Cerebral (n = 8)**	**Imaging (n = 11)**	**Peripheral (n = 1)**	**Polyvascular (n = 10)**
Male sex, n (%)	225 (78.1)	8 (100)	10 (91)	0 (0)	5 (50)
Age (years), mean ± SD	58.9 ± 9.8	55.7 ± 8.2	50.7 ± 8.8	62 ± 0	61.4 ± 15.3
Hypertension, n (%)	160 (55.5)	6 (75)	5 (45.4)	0 (0)	7 (70)
Diabetes, n (%)	100 (34.7)	4 (50)	1 (9)	0 (0)	5 (50)
BMI (kg/m^2), mean ± SD	24.9 ± 3.5	26.1 ± 7	27 ± 2.1	N/A	26.1 ± 5.6
Familial hypercholesterolemia, n (%)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
LDL-C (mg/dL), mean ± SD	104.2 ± 43.1	190.5 ± 79.3	159.6 ± 33.9	137 ± 0	107 ± 29.9
non-HDL (mg/dL), mean ± SD	134.7 ± 86.7	207 ± 83	170 ± 37	N/A	144.7 ± 30.7
Recruitment center, n (%)					
Java Island	127 (44.1)	8 (100)	10 (90)	1 (100)	4 (40)
Other islands	161 (55.9)	0 (0)	1 (9)	0 (0)	6 (60)

*Coronary = ACS, stable angina, coronary revascularizations; cerebral = stroke, TIA; clinical = did not fall into any diagnoses but presence of atherosclerotic plaques confirmed by imaging; peripheral = PAD; polyvascular = diagnoses involving more than one category from coronary, cerebral, or peripheral.

In the coronary-related group, one-third of the population had diabetes, and hypertension was present in more than half of them. LDL-C level averaged more than 100 mg/dL in all ASCVD groups, with higher average LDL-C observed in non-coronary related ASCVD.

Table 3 provides baseline characteristics in accordance with payment status. Mean age was highest in the out-of-pocket group (62.4 years), followed by JKN (59 years) and private insurance (49.9 years), suggesting that privately insured patients may represent a younger cohort. JKN patients were predominantly recruited from public hospitals, such as Prof. Dr. W.Z. Johannes General Hospital (31.2%) and Zainoel Abidin General Hospital (22.5%). Private insurance patients were concentrated at Pertamina Hospital Center (68.2%), whereas out-of-pocket patients were largely recruited from Siloam Hospital Lippo Village (83.3%). High-intensity statin use was reported in 88 (34.8%) of JKN patients, 17 (77.3%) of private insurance patients, and 13 (43.3%) of out-of-pocket patients. Use of other LLTs (e.g., ezetimibe) was exclusively seen in the out-of-pocket group, with 5 patients (16.7%) using ezetimibe and 1 (3.3%) using fenofibrate.

The recommended duration for repeat LDL-C measurement is 4-12 weeks after statin is initiated or an adjustment in dosage is made, followed by 3 to 12 months as needed. Assessment is required to measure LDL-C percentage changes from baseline in response to LLT to achieve LDL goals in accordance with the patient's cardiovascular risk.[6] Tables 4 to 6 provide LDL-C achievements over the visiting period in the outpatient clinic. At the first visit, most patients with ASCVD (78.8%) had LDL-C levels above 70 mg/dL, with a mean LDL-C of 108.4 mg/dL. Only 4.9% achieved LDL-C levels below 55 mg/dL. High-intensity statin users had the highest mean LDL-C (115.9 mg/dL), with 32% having levels above 70 mg/dL. Moderate-intensity users had a lower mean LDL-C (98.7 mg/dL), while low-intensity users exhibited the highest mean LDL-C (140.2 mg/dL), though they constituted a small subgroup.

Patients with private insurance showed the highest mean LDL-C (138.9 mg/dL), with 5.6% above 70 mg/dL. National health insurance (JKN) participants had a lower mean LDL-C (105.8 mg/dL), with a slightly better achievement of <55 mg/dL (4.2%). Patients with higher income levels (>25 million IDR) had a higher mean LDL-C (126.8 mg/dL) than middle-income (113.9 mg/dL) and low-income groups (107.3 mg/dL). Recruitment centers on Java Island had a slightly higher mean LDL-C (111.1 mg/dL) compared to other islands (105.5 mg/dL).

At the second outpatient visit (Table 5), moderate-intensity statin users showed a mean LDL-C of 91.4 mg/dL, while high-intensity users had a comparable mean of 90.6 mg/dL. No data were available for low-intensity statin users. The mean LDL-C was lowest among out-of-pocket payers (75 mg/dL), followed by JKN participants (93.5 mg/dL) and private insurance holders (92.1 mg/dL). High-income patients had the lowest mean LDL-C (82 mg/dL), followed by low-income (91.2 mg/dL) and middle-income groups (98.1 mg/dL). LDL-C levels were similar between Java Island (mean: 90.4 mg/dL) and other islands (mean: 91.8 mg/dL), with a slightly higher proportion of patients achieving <55 mg/dL on Java (3.6% vs. 4.5%).

Table 3. Baseline characteristics according to payment status.

Characteristics	Payment Status		
	JKN (n = 253)	**Private insurance (n = 22)**	**Out-of-pocket (n = 30)**
Male sex, n (%)	190 (75)	20 (91)	25 (83.3)
Age (years), mean ± SD	59 ± 9.8	49.9 ± 9.9	62.4 ± 9.2
Hypertension, n (%)	135 (53.3)	14 (63.6)	20 (0.67)
Diabetes, n (%)	84 (33.2)	7 (31.8)	11 (36.6)
Smoker, n (%)	136 (53.7)	10 (45.4)	7 (23.3)
LDL-C (mg/dL), mean ± SD	105.8 ± 42.3	138.9 ± 74.8	108.2 ± 40.2
Cardiovascular risk, n (%)			
Very high-risk	251 (99.2)	22 (100)	30 (100)
High-risk	2 (0.8)	0 (0)	0 (0)
Recruitment center, n (%)			
Java Island	88 (34.7)	22 (100)	30 (100)
Other islands	165 (65.2)	0 (0)	0 (0)
Statin intensity, n (%)			
High	88 (34.7)	17 (77.2)	13 (43.3)
Moderate	142 (56.1)	5 (22.7)	17 (56.7)
Low	4 (1.5)	0 (0)	0 (0)
No previous statin use, n (%)	2 (0.7)	0 (0)	0 (0)
Use of other LLTs, n (%)			
Ezetimibe	0 (0)	0 (0)	5 (16.7)
Fenofibrate	10 (3.9)	1 (4.5)	1 (3.3)

Table 4. Baseline LDL-C level at first visit.

Characteristics	n	LDL-C level (mg/dL)			
		<55	55-70	>70	Mean ± SD
With ASCVD, n (%)	302	15 (4.9)	49 (16.2)	238 (78.8)	108.4 ± 46.3
Statin intensity, n (%)					
High		7 (2.4)	18 (6.2)	92 (32)	115.9 ± 53.2
Moderate	287	8 (2.7)	29 (10.1)	127 (44.2)	98.7 ± 33.9
Low		0 (0)	1 (0.3)	3 (1)	140.2 ± 105.2
Payment status, n (%)					
National health insurance (JKN)		13 (4.2)	40 (13.1)	200 (65.7)	105.8 ± 42.3
Private insurance	304	2 (0.6)	3 (0.9)	17 (5.6)	138.9 ± 74.8
Out-of-pocket		0 (0)	6 (1.9)	23 (7.5)	108.2 ± 40.2
Monthly income, n (%)					
High (>25 million IDR)		0 (0)	0 (0)	9 (3.3)	126.8 ± 37.9
Middle (5-25 million IDR)	269	1 (0.3)	9 (3.3)	51 (18.9)	113.9 ± 47.9
Low (<5 million IDR)		12 (4.4)	34 (12.6)	153 (56.8)	107.3 ± 47.1
Location of recruitment center, n (%)					
Java Island	304	5 (1.6)	19 (6.2)	115 (37.8)	111.1 ± 49.7
Other islands		10 (3.2)	30 (9.8)	125 (41.1)	105.5 ± 43.7

*% is calculated from the total population per subgroup instead of the overall population due to missing data.

Table 5. LDL-C level at the second visit.

Characteristics	n per subgroup	LDL-C level (mg/dL)			
		<55	55-70	>70	Mean ± SD
Risk stratification					
Very high-risk	110	9 (8.1)	20 (18.1)	81 (73.6)	92.6 ± 34.3
High-risk		N/A**	N/A**	N/A**	N/A**
Statin intensity, n (%)					
High		1 (0.9)	9 (8.7)	22 (21.3)	90.6 ± 34.7
Moderate	103	7 (6.8)	10 (9.7)	54 (52.4)	91.4 ± 29.2
Low		N/A**	N/A**	N/A**	N/A**
Payment status, n (%)					
National health insurance (JKN)	110	9 (8.1)	12 (10.9)	72 (65.4)	93.5 ± 33.6
Private insurance		0 (0)	5 (4.5)	3 (2.7)	92.1 ± 53.5

Characteristics	n per subgroup	LDL-C level (mg/dL)			
		<55	55-70	>70	Mean ± SD
Out-of-pocket		0 (0)	3 (2.7)	6 (5.4)	75 ± 32.1
Monthly income, n (%)					
High (>25 million IDR)		0 (0)	1 (1)	2 (2)	82 ± 25.7
Middle (5-25 million IDR)	99	2 (2)	8 (8)	17 (17.1)	98.1 ± 47.3
Low (<5 million IDR)		7 (7)	9 (9)	53 (53.5)	91.2 ± 30.2
Location of recruitment center, n (%)					
Java Island	110	4 (3.6)	13 (11.8)	49 (44.5)	90.4 ± 37.8
Other islands		5 (4.5)	7 (6.3)	32 (29)	91.8 ± 33.7

*% is calculated from the total population per subgroup instead of the overall population due to missing data.
**N/A: No patients had LDL-C checked during the visit.

Table 6. LDL-C level at the third visit.

Characteristics	n	LDL-C level (mg/dL)			
		<55	55-70	>70	Mean ± SD
Risk stratification					
Very high-risk	94	5 (5.3)	15 (15.9)	73 (77.6)	96.9 ± 33.1
High-risk		0 (0)	0 (0)	1 (1)	122 ± 0
Statin intensity, n (%)					
High		2 (2.3)	4 (4.7)	41 (48.2)	92.6 ± 29.2
Moderate	85	2 (2.3)	6 (7)	29 (34.1)	104.3 ± 36.6
Low		0 (0)	1 (1.1)	0 (0)	57 ± 0
Payment status, n (%)					
National health insurance (JKN)		5 (5.3)	10 (10.6)	64 (68)	98.9 ± 32.8
Private insurance	94	0 (0)	4 (4.2)	2 (2.1)	69.8 ± 12.2
Out-of-pocket		0 (0)	1 (1)	8 (8.5)	107.6 ± 37.7
Monthly income, n (%)					
High (>25 million IDR)		0 (0)	0 (0)	2 (2.3)	101.5 ± 19
Middle (5-25 million IDR)	85	3 (3.5)	4 (4.7)	18 (21.1)	92.8 ± 39.3
Low (<5 million IDR)		2 (2.3)	9 (10.5)	47 (55.2)	98.2 ± 29.7
Location of recruitment center, n (%)					
Java Island	89	2 (2.2)	4 (4.5)	47 (52.8)	96.7 ± 30.2
Other islands		3 (3.3)	6 (6.7)	27 (30.3)	97.8 ± 37.7

*% is calculated from the total population per subgroup instead of the overall population due to missing data

Table 7. Missed visits within each follow-up.

Characteristics	First visit	Second visit	Third visit
Missed visits, n (% per total population)	17 (5.2)	119 (36.9)	183 (57.5)
Age, mean ± SD	60.2 ± 9.3	59.2 ± 10.4	58.7 ± 9.9
Payment status, n (%)			
National health insurance (JKN)	N/A	76 (63.8)	118 (64.4)
Private insurance	N/A	11 (9.2)	6 (3.2)
Out-of-pocket	N/A	15 (12.6)	11 (6)
Monthly income, n (%)			
High (>25 million IDR)	N/A	6 (5)	7 (3.8)
Middle (5-25 million IDR)	N/A	17 (14.2)	32 (17.4)
Low (<5 million IDR)	N/A	60 (50.4)	107 (58.4)
Location of recruitment center, n (%)			
Java island	11 (3.6)	59 (49.5)	90 (49.1)
Other islands	6 (1.9)	60 (50.4)	93 (50.8)

Table 8. LDL-C level trend during visits.

Characteristics	LDL-C level (mg/dL), mean ± SD		
	First visit	Second visit	Third visit
Overall	108.1 ± 46.6	92.6 ± 34.3	97.2 ± 33.1
Payment status			
JKN	105.8 ± 42.3	93.5 ± 33.6	98.9 ± 32.8
Non-JKN	121.5 ± 59.1	87.4 ± 38.3	92.5 ± 35.1
ASCVD type			
Coronary	104.4 ± 42.7	91.3 ± 33.2	96.5 ± 33.6
Non-coronary	228.6 ± 26.6	63 ± 0	77 ± 0
Geographical location			
Java Island	111.1 ± 49.7	90.4 ± 37.8	96.7 ± 30.2
Other islands	105.5 ± 43.7	91.8 ± 33.7	97.8 ± 37.7

At the third outpatient visit (Table 6), patients on high-intensity statins had a mean LDL-C of 92.6 mg/dL, while those on moderate-intensity regimens had a higher mean of 104.3 mg/dL. No patients on low-intensity statins had LDL-C measured. Out-of-pocket payers had the highest mean LDL-C (107.6 mg/dL) compared to JKN participants (98.9 mg/dL) and private insurance holders (69.8 mg/dL). The mean LDL-C was highest in high-income patients (101.5 mg/dL), followed by low-income (98.2 mg/dL) and middle-income (92.8 mg/dL) groups. Java Island centers

had a slightly lower mean LDL-C (96.7 mg/dL) compared to other islands (97.8 mg/dL).

Missed outpatient visit rates increased progressively over the follow-ups, from 5.2% at the first visit to 36.9% at the second visit, and 57.5% at the third visit. Patients covered by the National Health Insurance (JKN) accounted for the majority of missed visits at both the second (63.8%) and third (64.4%) follow-ups. Patients with low income (<5 million IDR) consistently constituted the largest proportion of missed visits, comprising 50.4% at the second visit and 58.4% at the third visit. High-income patients (>25 million IDR) had the lowest rates of missed visits, contributing to 5% and 3.8% at the second and third visits, respectively. Missed visits were nearly evenly distributed between Java Island and other islands at both the second (49.5% vs. 50.4%) and third follow-ups (49.1% vs. 50.8%).

Discussion

In adherence to Indonesian recent guidelines for dyslipidemia management, very high-risk patients should aim to achieve an LDL-C level lower than 55 mg/dL, while high-risk patients should achieve an LDL-C of 70 mg/dL or lower.[8] In this study, only 4.6% of the population managed to achieve LDL-C below 55 mg/dL, and 19.8% achieved LDL-C 70 mg/dL or lower, exhibiting that the overall proportion of patients achieving target LDL-C was persistently low. The low rate of LDL-C target achievement in the very high-risk population is consistent with findings from other observational studies. OneACS registry in Indonesia reported that only half of the study population (54.7%) received high-intensity statin as part of routine medication despite being stratified as very high-risk and having g high LDL-C baseline at a median of 115 mg/dL.[9] Lp(a) and ApoB were only measured in a small subset of patients. Despite playing a role in determining cardiovascular risk, both parameters are not affected by LLTs and are not part of lipid therapy targets, hence the lack of need for evaluation. Unavailability of Lp(a) and ApoB standardized assays in public laboratories service covered by JKN also contributed to this, as most of the subjects utilize JKN.

Socioeconomic disparities significantly influenced LDL-C outcomes. Socio-economic factors should be considered in issuing public health policy, in addition to ASCVD traditional risk factors.[10] Private insurance patients demonstrated the most notable improvements, achieving an average LDL-C reduction of 61.2 mg/dL by the third visit compared to 33.7 mg/dL in JKN patients and 41.8 mg/dL in out-of-pocket patients. This group showed a nearly fourfold reduction at the second visit compared to JKN participants and a 1.5 times greater reduction than out-of-pocket patients. By the third visit, private insurance patients achieved a mean LDL-C level of 69.8 mg/dL, successfully meeting the high-risk LDL target, while JKN patients remained at 98.9 mg/dL on average.

In contrast, JKN patients exhibited slower, more gradual improvements. While LDL-C levels decreased modestly across visits, 82.2% of this group failed to achieve LDL-C <70 mg/dL by the third visit. These outcomes reflect systemic barriers within the national health insurance system, which may include limited access to high-intensity statins and restricted availability of statin adjuvants. Out-of-pocket patients showed inconsistent LDL-C control, with a mean LDL-C reduction of 41.8 mg/dL by the third visit. Despite this improvement, financial constraints likely contributed to poor adherence to medications and follow-up care, as evidenced by the highest rate of missed visits in this group.

Patients from islands outside Java were prescribed fewer high-intensity statins. Report from the Indonesian Ministry of Health showed uneven distribution of utilization of cardiovascular specialist services, mostly concentrated in West, East, and Central Java, while Papua, North Borneo, West Sulawesi, and Maluku have a low number of service users. Cardiovascular specialist services were only available in some secondary and tertiary healthcare facilities, indicating that the eastern region had very limited access to such care and relied heavily on primary healthcare facilities.[4] Despite the limitations, patients from islands outside Java achieved slightly higher proportions of LDL-C <55 mg/dL at all visits compared to those on Java Island, showing a slight difference in LDL-C achievement between these two geographical areas.

Statin intensity was closely linked with LDL-C outcomes. Patients receiving high-intensity statins achieved better results, with LDL-C reductions averaging 60.5 mg/dL by the third visit, compared to 34.7 mg/dL for moderate-intensity statins and 20.1 mg/dL for low-intensity regimens. Among patients achieving LDL-C <55 mg/dL, 20% were on high-intensity statins, underscoring their importance in achieving guideline-recommended targets.

However, access to high-intensity statins was uneven across socioeconomic groups. Only 15.6% of JKN patients and 20% of out-of-pocket patients

were prescribed high-intensity statins, compared to 33.3% of private insurance patients. This disparity highlights the systemic barriers within the JKN framework, and the financial challenges faced by out-of-pocket patients. Previous data have revealed that guideline-directed medical treatment can mitigate ASCVD risk for future events.[11]

Missed visits increased substantially over time, with 57.5% of patients failing to attend the third visit. This trend was most pronounced among JKN patients and those with low monthly incomes, suggesting systemic inefficiencies and financial constraints. For instance, missed visits in JKN patients rose from 37.4% at the second visit to 64.4% at the third visit, compared to private insurance patients, where missed visits were consistently lower (9.2% and 6%, respectively).

Geographical barriers also contributed, as patients from islands outside Java had higher missed visit rates, particularly at the third visit (50.8% versus 49.1% for Java). Limited healthcare infrastructure and long travel distances likely exacerbated this issue.

Interestingly, higher-income groups exhibited poorer LDL-C control despite access to better resources. These patients showed less pronounced LDL-C reductions, potentially reflecting differences in adherence, dietary habits, or prioritization of preventive care. In contrast, lower-income patients on JKN coverage demonstrated gradual but consistent LDL-C reductions, averaging 33.7 mg/dL by the third visit. This paradox highlights the complex interplay between socioeconomic status, behavior, and healthcare outcomes.

Study limitations

Several limitations were identified in this study. First, the geographical scope only included 6 out of 34 provinces in Indonesia, covering only Java, Sumatra, and several eastern small islands, which may not represent the actual diversity of healthcare practices and patient populations across the entire country. The relatively small sample population also limited the statistical power of the study and may impact the reliability of subgroup analyses. Some patients were lost to follow-up during the study. There was also an imbalance in the number of patients after being classified into several factors. This disparity may have affected the analysis and the ability to draw definitive conclusions about differences between these compared groups. Moreover, intergroup statistical analyses were not performed due to the study's descriptive design and limited sample size.

Conclusion

The majority of the population failed to achieve the recommended target LDL-C levels. There is a significant gap in statin prescription contributed by socioeconomic factors for cholesterol management in Indonesia. These findings underscore the need for comprehensive efforts to improve LDL-C goal attainment, optimize the use of high-intensity statin therapy and its adjuvants by formulating strategies in consideration of the JKN framework and healthcare access. Such measures are crucial to enhancing outcomes and reducing cardiovascular burden for high-risk populations in Indonesia.

List of Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
BPS	*Badan Pusat Statistik* (Central Bureau of Statistics)
CVD	Cardiovascular disease
ESC	European Society of Cardiology
IDR	Indonesian Rupiah
JKN	*Jaminan Kesehatan Nasional* (National Health Insurance)
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid-lowering therapy

Ethical Clearance

The study was approved by the Ethics Board Committee of all respective centers where the research was conducted. Informed consent in written form was obtained from each participant prior to the data collection.

Publication Approval

All authors consent to the publication of this manuscript.

Authors' Contributions

All authors contributed to the study development, data collection, data analysis, and manuscript development.

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Conflict of Interest

The authors declared that they have no competing interests.

Availability of Data and Materials

Datasets are owned and kept by the Indonesian Heart Association's (PERKI) Working Group of Atherosclerosis, Thrombosis, Lipidology, and Regenerative Therapy (ATLR).

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Original Article

Comparison of right ventricular global longitudinal strain between pacemaker lead position in patients with permanent pacemaker

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Abstract

Background: The implantation of a permanent pacemaker (PPM) can reduce right ventricular function. Echocardiography using speckle tracking can detect a decrease in right ventricular function earlier. The value of right ventricular global longitudinal strain (RVGLS) based on the location of the pacemaker lead between the apex and non-apex was currently unknown, although the placement of the correct pacemaker lead location was very important for evaluating right ventricular dysfunction to prevent right heart failure. This study aims to determine the comparison of RVGLS between pacemaker lead positions in patients with a permanent pacemaker.

Methods: This study was a nested case-control study to assess the comparison of RVGLS between pacemaker lead positions in patients with a permanent pacemaker. The study was divided into the right ventricular apex group (RVA) and the non-right ventricular apex group (NRVA). This study used data from the pacemaker registry and medical records of patients who had undergone pacemaker implantation since June 2021. The Shapiro-Wilk normality test was performed before analyzing all numerical data, followed by an independent t-test or Mann-Whitney test to determine the differences between groups.

Results: In this study, there were 38 patients with permanent pacemakers, consisting of 18 samples with the RVA group and 20 samples with the NRVA group. In this study, no significant differences were found in age, sex, diagnosis, comorbidities, therapy, pacemaker mode, baseline QRS duration, pacing burden, puncture site, and initial echocardiography between of two groups. There was a significant difference in paced QRS duration between the RVA and RVNA groups (160 + 20 ms vs 140 + 28 ms, p=0.024). Based on statistical analysis, there was a significant difference in the value of RVGLS in the RVA group compared to the RVNA group (-14.87 + 4.48% vs -18.40 + 3.21%, p=0.015).

Conclusions: The position of the apex right ventricular lead resulted in a lower value of RVGLS compared to the position of the non-apex right ventricular lead.

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Keywords: *Pacemaker lead, right ventricular function, right ventricular global longitudinal strain.*

Introduction

The prevalence of permanent pacemakers is estimated to reach 1.25 million each year worldwide. In 2016, there were 500,000 pacemaker implantations in Europe. In Indonesia, the Asia Pacific Heart Rhythm Association (APHRS) reported 1,342 permanent pacemaker implantations in 2021.[1-2] Long-term effects of pacemaker implantation were heart failure, atrial fibrillation, increased mortality, and morbidity. The incidence of right heart failure has been reported at 22% cases after one year of pacemaker implantation. The mechanism of right ventricular dysfunction in permanent pacemakers is debatable to this day.[3-4] Several studies have shown that the position of the pacemaker lead in the right ventricular apex is associated with the occurrence of right heart failure. A study by Yu et al. showed that lead-associated tricuspid regurgitation and electrical asynchrony are higher at the right ventricular apex than at non-ventricular leads' apex.[5-6]

Early detection of right ventricular dysfunction was mandatory. Conventional echocardiography has some limitations, such as being operator-dependent, time-consuming, and detecting when it is clinically manifested.[7-8] The global longitudinal strain parameter of the right ventricle with speckle tracking echocardiography has been reported to be able to detect the presence of subclinical right ventricular dysfunction earlier and more sensitively than conventional parameters.[8-10]

The value of global longitudinal strain based on the location of the pacemaker lead between the apex and non-apex is still unknown; on the other hand, the placement of the correct lead location is essential for evaluating right ventricular dysfunction to prevent right heart failure. This study aims to determine the comparison of RVGLS between pacemaker lead positions in permanent pacemaker patients.

Methods

This was a nested case-control study for the determination of comparison of RVGLS between pacemaker lead positions in patients who underwent pacemaker implantation from June 2021 to October 2023. Inclusion criteria were patients who had an echocardiography initial due to permanent pacemaker implantation (PPI) and echocardiography data after 6-12 months of PPI. We exclude patients with LV and RV dysfunction at echocardiography, significant valve disease, history of tachyarrhythmia, documented acute coronary syndrome during PPI, and poor echocardiographic windows.

Study Population

The total population was 83 patients. There are 51 patients who met the inclusion criteria. Three samples were excluded because the ejection fraction function on the initial echocardiogram was below 50%. The samples that were excluded were 2 samples in the RVA group and 1 sample in the NRVA group. In order to have the same number of samples and follow the required sample size according to the sample size formula, a random sampling was carried out in the NRVA group using the Microsoft Excel application with the RANDBETWEEN formula for 20 samples, so that the total sample in the study was 38 samples.

Pacing Procedure

Patients underwent dual-chamber or single-chamber implantation by operator preference under fluoroscopy in the catheterization laboratory. Pacemaker leads were inserted using a subclavian venous, axillary venous, or cephalic venous cutdown approach. Right atrial leads were implanted in the RA appendage, RV leads were implanted in the RV apex groups or the non-RV apex group (RVOT, Septal, and His-Bundle). Pacing burden was measured at interrogate evaluation 6-12 month after PPI.

ECG and Echocardiography

Standard echocardiography was performed using Vivid 7 Ultrasound with a 3.5 MHz multiphase-array probe. Patients are in the lateral decubitus position on the left. The 2D-guided M-mode method was used to determine chamber dimensions, while the Simpson's method was used to measure LVEF. 2D RV pictures were obtained from apical four-chamber or RV focus views. We measured the tricuspid annulus's Doppler imaging systolic velocity. The average segmental strain was used to determine the GLS. The endocardial border along the RV apex and the free wall to the tricuspid valve annulus were identified, and the RV peak systolic longitudinal strain was calculated using an interface. The program automatically separates three RV free wall and three septal wall segments and calculates the longitudinal peak systolic strain; the RVGLS was determined as the average of these longitudinal peak systolic strains after a region of interest covering the breadth of the myocardium was defined.

Statistical Analysis

Data with normal distribution are presented as mean value ± SD. Data with abnormal distribution are presented as median and minimum-maximum. The chi-square test was used to compare categorical data. An unpaired t-test was performed

on numeric data with normal distribution. Mann-Whitney was performed on numeric data with abnormal distribution. A P-value <0.05 was considered statistically significant. Bland-Altman method of comparison was used to assess inter-observer variability. The analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Mac version 25.

Results

Patients Clinical Characteristic

The baseline characteristics of the study population are shown in Table 1. Paced QRS duration of the RVA group after evaluation (6-12 months after PPI) was significantly different from the NRVA group with p=0.024. The baseline values of LVEF, TAPSE, and RVGLS did not differ substantially between the two groups.

Comparison of echocardiographic values of the RVA pacemaker group and the NRVA pacemaker group

According to Table 2, the RVGLS of the NRVA group is higher than the RVGLS of the RVA group with a p-value of 0.015; this difference is statistically significant. Table 2 also explains that there were no significant differences in the values between the RVA and NRVA groups on other echocardiographic parameters such as LVEF, TAPSE, RV FAC, RVS', PAcct, TRV, TVG, PVR, RA area, RV basal diameter, and severity of TR.

Intra-observer and inter-observer variability

The evaluation of intra-observer and inter-observer variability using the Bland-Altman method showed good agreement in the examination of global longitudinal strain of the right ventricle. No significant differences were found between intra- and inter-observer (p>0.05), and the data were 100% within the 95% limit of agreement.

Table 1. Baseline characteristics.

Variable	RVA (n = 18)	NRVA (n = 20)	p-value
Age (year), median (minimum-maximum)	61 (49-85)	62 (20-81)	0.661[b]
Sex, n (%)			
Male	4 (22)	8 (40)	0.307[a]
Female	14 (78)	12 (60)	
Pacing indication, n (%)			
Sinus node dysfunction (SND)	5 (27)	6 (30)	0.880[a]
AV block	13 (73)	14 (70)	
Co-morbid risk factor, n (%)			
Hypertension	8 (44)	11 (55)	0.516[a]
Diabetes Mellitus	4 (22)	2 (10)	0.395[a]
Dyslipidemia	6 (33)	4 (20)	0.287[a]
Smoker	2 (11)	5 (25)	0.410[a]
Medication, n (%)			
Angiotensin converting enzyme inhibitor (ACE-I)	3 (16)	2 (10)	0.448[a]
Angiotensin receptor blocker (ARB)	5 (27)	9 (45)	0.272[a]
B-blocker			
Calcium channel blocker	6 (33)	7 (35)	0.914[a]
Statin	2 (11)	4 (20)	0.663[a]
Antiplatelet	2 (11)	2 (10)	1.000[a]
Diuretic	0	2 (10)	0.488[a]
Pacing Mode, n (%)	2 (11)	2 (10)	1.000[a]
VVI	13 (72)	17 (85)	0.438[a]
DDD	5 (27)	3 (15)	
ECG: QRS duration (ms)			
Baseline QRS duration, median (minimum-maximum)	80 (40-120)	80 (40-120)	1.000[b]
Paced QRS duration after implant, median (minimum-maximum)	160 (80-180)	140 (60-160)	**0.024[b]**
Pacing burden, n (%)			
≤ 50%	6 (33)	3 (15)	0.260[a]
> 50%	12 (67)	17 (85)	

Variable	RVA (n = 18)	NRVA (n = 20)	p-value
Site Puncture, n (%)			
V. Subclavia	16 (88)	13 (65)	0.074[a]
V. Aksilaris	2 (12)	2 (10)	
V. Cephalica	0	5 (25)	
Echocardiography baseline			
LV EF (%), mean±SD	59.50 ± 10.58	63.55 ± 8.31	0.196[c]
TAPSE (cm), mean±SD	2.13 ± 0.35	2.08 ± 0.30	0.618[c]
Right ventricular global longitudinal strain (%), median (minimum-maximum)	-21.50 (-20 up to -24.5)	-21.5 (-20.2 up to -23.5)	0.736[b]

[a]chi square test
[b]Mann-Whitney test
[c]Independent sample t-test

Table 2. Echocardiography of the pacemaker lead on follow-up.

Variable	RVA (n = 18)	NRVA (n = 20)	p-value
LV EF (%), mean±SD	62.56 ± 6.50	64.55 ± 6.31	0.344[c]
Right ventricular global longitudinal (%), mean±SD	-14.87 ± 4.48	-18.40 ± 3.21	**0.015[c]***
TAPSE (cm), mean±SD	2.08 ± 0.31	2.33 ± 0.49	0.073[c]
RV FAC (%), median (minimum-maximum)	44 (35-54)	47.50 (36-73)	0.341[b]
RVS' (cm/s), median (minimum-maximum)	12 (10-14)	12 (10-21)	0.201[b]
PAccT (ms), mean±SD	111.39 ± 24.9	123.35 ± 23.12	0.134[c]
TR Vmax (m/s), median (minimum-maximum)	2.15 (1.2-3.3)	2.1 (1.2-2.9)	0.297[b]
TVG (mmHg), median (minimum-maximum)	19 (6-43)	19.06 (6-68)	0.608[b]
PVR, mean±SD	2.05 ± 0.32	1.92 ± 0.69	0.475[c]
RA area, mean±SD	20.23 ± 3.04	18.49 ± 5.93	0.269[c]
RV basal diameter, mean±SD	34.83 ± 5.75	37.25 ± 5.62	0.199[c]
TR severity			
Mild	17	20	0.474
Moderate	1	-	
Severe	-	-	

[b]Mann-Whitney test
[c]Independent sample t-test

Discussion

This study showed that there were differences in the values of RVGLS in the groups of right ventricular apex pacemakers and non-right ventricular apex pacemakers, with an average value of -14.87 ± 4.48% in the RVA group and -18.40 ± 3.21% in the NRVA group. The results of this study are also supported by the results of study by Solima, et al., which reported a decrease in global longitudinal strain of the right ventricle after 6 months of RVA pacemaker implantation compared to the control group with a value of right ventricular GLS of -14.623 ± 4.295% compared to

the control group with a value of right ventricular GLS of -20.37 ± 1.987%.[11]

Several studies have also reported a decrease in right ventricular function after permanent pacemaker implantation. A study by Sinkar et al. reported a decrease in RVEF of 2.8% after 6 months of RVA pacemaker implantation. A study by Gupta et al. reported a decrease in right ventricular myocardial performance index and TAPSE after 6 months of RVA pacemaker implantation. These studies concluded that there is a decrease in right ventricular function in RVA pacemakers based on the assessment of right ventricular function by conventional echocardiography. Several studies have reported that a decrease in right ventricular function is associated with electrical asynchrony, mechanical asynchrony, and lead-associated tricuspid regurgitation.[3-4]

A study by Soliman et al. showed that right ventricular dysfunction is associated with electromechanical changes, such as a decrease in conduction velocity and mechanical asynchrony. Right ventricular apex pacemakers also cause faster activation in the apical segment and slowing in the basal segment, resulting in decreased right ventricular function, also known as intraventricular asynchrony. Because a significant difference in QRS duration was found in the RVA and NRVA groups (160 + 20 ms in RVA and 140 + 28 ms in NRVA) after implantation of permanent pacemakers, intraventricular asynchrony could be one of the factors causing a decrease in global longitudinal strain of the right ventricle in this study.[11]

Other studies also show that right ventricular apex pacemakers have a wider QRS duration, resulting in more non-physiological ventricular activation, mechanical asynchrony, electrical asynchrony, higher myocardial perfusion defects, and decreased right ventricular function. Electrical impulses from right ventricular pacemakers originate from the right ventricle and spread through the myocardium, not through the His-Purkinje conduction system, resulting in a wider QRS complex like in LBBB. Pacemakers with wider QRS will increase the risk of heart failure compared to patients with narrower QRS, so the selection of non-right ventricular apex pacemakers is preferred in the prevention of long-term comorbidities.[10, 12-13]

A study by Yu YJ, et al., reported a higher risk of tricuspid regurgitation in the RVA group compared to the NRVA group due to lead impact with the posterior valve. However, this was not found in this study because there was no statistically significant difference in the degree of tricuspid regurgitation in both groups. This may be because the study by Yu YJ, et al., conducted an echocardiographic evaluation with a longer duration of up to 55 months in the RVA group.[6]

There were no statistically significant differences in conventional echocardiographic parameters during evaluation in the RVA and NRVA groups. The results of a study by Yu YJ, et al., showed that there were no statistically significant differences in conventional right ventricular function in the RVA and NRVA groups after pacemaker implantation. A study by Chen JY, et al., also showed that there were no differences in conventional right ventricular function values in patients with apical and septal pacemaker lead implantation after 3-6 months.[6, 14]

Beyond early subclinical changes detected by strain, several studies suggest that right-ventricular apical (RVA) pacing may carry less favorable long-term consequences compared with non-apical sites. RVA pacing has been associated with wider QRS and greater electromechanical desynchrony, factors linked to adverse remodeling and progression of tricuspid regurgitation (TR) due to lead–leaflet interaction and altered RV mechanics.[5-6] Comparative data also indicate better mechanical performance with non-apical sites such as septal/RVOT pacing,[12] while experimental work shows early maladaptive molecular changes after RVA pacing that plausibly precede clinical dysfunction.[13] Although our study was not powered for clinical endpoints, the lower (less negative) RVGLS in the RVA group is consistent with these mechanistic concerns and may represent an early marker of subsequent adverse remodeling.

This study is the first study to assess the differences in global longitudinal strain values of the right ventricle in patients with RVA pacemakers and NRVA pacemakers in Indonesia. The results of this study are expected to be used as a basis for further research on the relationship between the position of the pacemaker lead and right heart function over a longer period of time and with a larger sample size, making it one of the efforts to conduct early screening to prevent the occurrence of heart failure in patients with permanent pacemakers. This study is also expected to help clinicians in choosing the position of the pacemaker lead in pacemaker implantation.

Limitations

Although this study has shown differences in the values of global longitudinal strain of the right ventricle based on the position of the permanent pacemaker lead, the researchers are aware that there are still some shortcomings in this study. In

this study, our follow-up was limited to 6–12 months, and we did not collect long-term clinical outcomes (e.g., heart failure hospitalization, mortality), serial TR progression, or pacing-induced cardiomyopathy. As such, we cannot determine whether the observed RVGLS differences translate into long-term adverse events or clinically significant TR. The sample size and single-center design further limit the detection of infrequent outcomes. The ECG conditions at the time of the echocardiographic examination were not differentiated, whether in the condition of ECG pacing or ECG on beat. This study also did not assess the interrogate characteristics in patients with pacemakers, such as impedance values, R wave, and amplitude.

Conclusion

Our study compared right ventricular global longitudinal strain between the RVA and NRVA groups. There were no significant differences of characteristic groups except for paced QRS duration between the right ventricular apex pacemaker group and the non-right ventricular apex pacemaker group. The right ventricular apex pacemaker groups have lower global longitudinal strain values than the non-right ventricular apex pacemaker groups.

List of Abbreviations

APHRS	Asia Pacific Heart Rhythm Society
ECG	Electrocardiography
LVEF	Left Ventricular Ejection Fraction
NRVA	Non-Right Ventricular Apex
PPI	Permanent Pacemaker Implantation
PPM	Permanent Pacemaker
PVR	Pulmonary Vascular Resistance
RVA	Right Ventricular Apex
RVFAC	Right Ventricular Fractional Area Change
RVGLS	Right Ventricular Global Longitudinal Strain
RVOT	Right Ventricular Outflow Tract
TAPSE	Tricuspid Annular Plane Systolic Excursion
TR	Tricuspid Regurgitation

Ethical Clearance

All methods were carried out by relevant guidelines and regulations after obtaining approval and recommendations from the Ethics Committee Review Board of Dr. M. Djamil General Hospital, with reference number LB.02.02/5.7/299/2023.

Publication Approval

All authors consent to the publication of this manuscript.

Authors' Contributions

MF contributed to the study's conception and design, data collection, analysis and interpretation, as well as drafting and critically revising the manuscript for important intellectual content. HER and MY provided critical supervision and intellectual input. RM offered supervision with a particular focus on statistical analysis and research methodology.

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Conflict of Interest

None.

Availability of Data and Materials

Not applicable.

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Review Article

Mexiletine in the treatment of LQT2, LQT3, and acquired LQTS: a meta-analysis

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Abstract

High mortality in patients with Long QT Syndrome (LQTS) can be reduced with proper treatment. Gene-specific therapy is crucial, as many treatments are not equally effective across different LQTS types. While mexiletine has been established in the treatment of LQT3, its use in other types of LQT needs further evaluation. A meta-analysis was conducted using systematic electronic searches of PubMed, Embase, and Cochrane Library. We assessed QTc reduction and cardiac events after Mexiletine treatment. Inclusion criteria: any study with no language restriction that diagnoses any type of LQTS, uses mexiletine treatment, and provides QTc comparison before and after treatment. Animal studies were excluded. The NIH Study Quality Assessment Tools and Newcastle-Ottawa Scale were used to evaluate bias. Data were analyzed using Review Manager 5.4 and MedCalc software. Nine studies (n=281) were included. Mexiletine reduced QTc by -64ms (mean difference [MD], -64.22; 95% confidence interval [CI] -76.13 to -52.30; p<.001; I^2 60%). Sensitivity and sub analyses showed consistent efficacy. In five studies (n=76), the number of patients with high-risk QTc (>500ms) significantly decreased (Risk Ratio [RR], 0.38; 95% CI 0.26-0.55; p<.001). Five studies (n=141) showed a significant reduction in cardiac events (RR, 0.25; 95% CI 0.14-0.44; p<.001). Two studies reported gastrointestinal (GI) problems and vertigo as side effects of mexiletine treatment. Mexiletine significantly reduces QTc and cardiac events in LQT2, LQT3, and aLQT patients. Mexiletine also significantly reduces the number of Long QT patients with high-risk QTc.

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Keywords: *Arrhythmia, Electrocardiography, Long QT syndrome, Mexiletine, QTc*

Introduction

QT prolongation on an ECG can induce cardiac events and fatal arrhythmias. The causes of Long QT Syndrome (LQTS) can be divided into congenital and acquired.[1] The congenital LQTS is a result of pathogenic variants in the genes encoding ion channels, which cause delayed inactivation or loss of channel function. Acquired LQTS (aLQT) can be caused by acquired mechanisms such as electrolyte imbalance, drugs, or secondary to other medical conditions.[2] The prevalence of congenital LQTS is estimated to be approximately 1 in 2,500 to 1 in 10,000 individuals and has a high mortality rate without proper treatment, up to 21% within 1 year from the first syncope episode, and can be reduced to approximately 1% during 15 years of follow-up with treatment.[1,3] Six genes (KCNQ1, CALM1, CALM2, CALM3, KCNH2, and SCN5A) are already known as definitive genes for typical LQTS, while one gene (TRDN) has been found to have strong evidence for causality in LQTS. Additionally, nine genes (CACNA1C, KCNJ2, CAV3, ANK2, SCN4B, SNTA1, KCNE2, AKAP9, KCNJ5) are classified as having limited or disputed evidence as causative of LQTS.[4] KCNE1 was classified as having only limited evidence, and KCNE2 as having disputed evidence for causality in LQTS; both genes were classified as having strong evidence for specific risk alleles in predisposing to aLQTS.[5]

Lifestyle changes, beta-blocker, left cardiac sympathetic denervation (LCSD), and ICD implantation are the mainstay treatments for LQTS.[6] Gene-specific therapy is highly important in LQTS treatment since beta-blockers are not equally effective in all types of LQT (LQT3>LQT2>LQT1).[3] Mexiletine, a class Ib sodium channel blocker, has been utilized to a limited extent in LQTS patients, especially in LQT3.[6-7] Mexiletine use in other types of LQT remains a question as newer studies continue to be conducted.[8-10] To further evaluate the effect of mexiletine in other types of LQT, we performed a meta-analysis of currently available journal/literature.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to ensure the reporting quality. A systematic electronic search of PubMed, Embase, and Cochrane Library was conducted from database inception to February 8, 2025, without any language restrictions. The keywords used in the literature search were mexiletine, long QT syndrome, LQTS, acquired long QT, and acquired QT. The search strings used were (Mexiletine) AND (Long QT Syndrome OR Long QT OR LQTS OR acquired long QT OR acquired QT prolongation).

Inclusion Criteria and Exclusion Criteria

The inclusion criteria were as follows: any study with no language restriction that (1) diagnoses LQTS based on guidelines, with any type of LQT; (2) uses mexiletine treatment, which can be administered via the oral or IV route, given as chronic or acute treatment, and used as either an add-on or sole treatment; and (3) compares QTc before and after treatment. The exclusion criterion was whether the study was performed in a human or animal heart model.

Data Extraction and Quality Assessment

The authors (DIR and MIQ) independently screened the title and abstract to remove duplicates and then continued to review the full text to confirm and select the studies based on predefined inclusion and exclusion criteria. If there is a disagreement between authors, a third opinion from another author (CJC) will be considered. A predefined standard data extraction form was used to collect information, including author name, year, study design, population, LQT type, sex, age, mexiletine dose, route of administration, treatment combination, QTc before and after treatment, and cardiac events, which were performed by one author (DIR) and verified by another author (CJC). The study quality was assessed using the National Institutes of Health Study Quality Assessment Tool and Newcastle-Ottawa Scale (NOS).

Statistical Analysis

All data analyses were performed using Review Manager 5.4 and MedCalc software. Statistical significance was set at a p-value <0.05 was considered significant. Heterogeneity was considered using I^2 values of approximately 5% – 50% (mild), 50%–75% (moderate), and >75% (severe). If heterogeneity was moderate or severe, a random-effects model was selected, followed by a sub-analysis and sensitivity analysis. The primary outcomes of this study were QTc (mean ± SD) and cardiac events (RR) after mexiletine treatment. If the summary statistics were shown as median and interquartile range (IQR), the values of mean ± SD were estimated following the Cochrane guidelines. Studies with missing data necessary for other analyses were excluded. A sub-analysis was also performed for each LQT type. This study is shown as a forest plot.

Results

Study Characteristics

The study selection process is shown in the PRISMA flow diagram (Figure 1). Of the 358 identified studies, 29 duplicates were excluded. A total of 329 articles underwent title and abstract screening by two independent authors, and 9 studies were selected based on predefined inclusion and exclusion criteria and were included in the meta-analysis. Studies included were three focused on LQT3[11-13], one focused on LQT2[10], one focused on acquired LQT[9], and four evaluated more than one type of LQT[14-17], including one LQT2 study that involved two patients with multiple types of LQTS-associated variants (one patient with a variant in KCNQ1-mediated LQT1 and one patient with a variant in SCN5A-mediated LQT3).[14] The total population of this study was 281 patients. The population characteristics of the included studies are presented in Table 1.

Reduction of QTc and Cardiac Events

From 9 studies (n = 281), we evaluated the effect of mexiletine in reducing QTc and the number of cardiac events.[9-17] Mexiletine significantly reduced QTc by approximately -64ms (mean difference [MD], -64.22; 95% confidence interval [CI] -76.13 to -52.30; p<0.001; I^2 60%) (Figure 2A). After conducting a sensitivity analysis by removing one outlier study[17], the pooled mean difference for the QTc interval reduction with mexiletine treatment remained significant (MD, -67.66; 95% CI -75.93 to -59.40; p<0.001; I^2 0%). Some studies did not provide all the necessary data; therefore, we only included studies that contained the required information for other analyses to prevent potential bias. Mexiletine responders were defined as those with a QTc reduction ≥ 40 ms.[10,14] In five studies[9-10,12,14-15] (n = 140), the prevalence of QT reduction ≥40 ms was 74% (proportion 0.74; CI 0.55-0.90) (Figure 2B). The high-risk QTc was defined as QTc >500 ms.[12,14,17] From 5 studies[9,11-12,14-15] (n = 76), 56 (73%) patients had QTc >500 ms. After mexiletine treatment, the number of

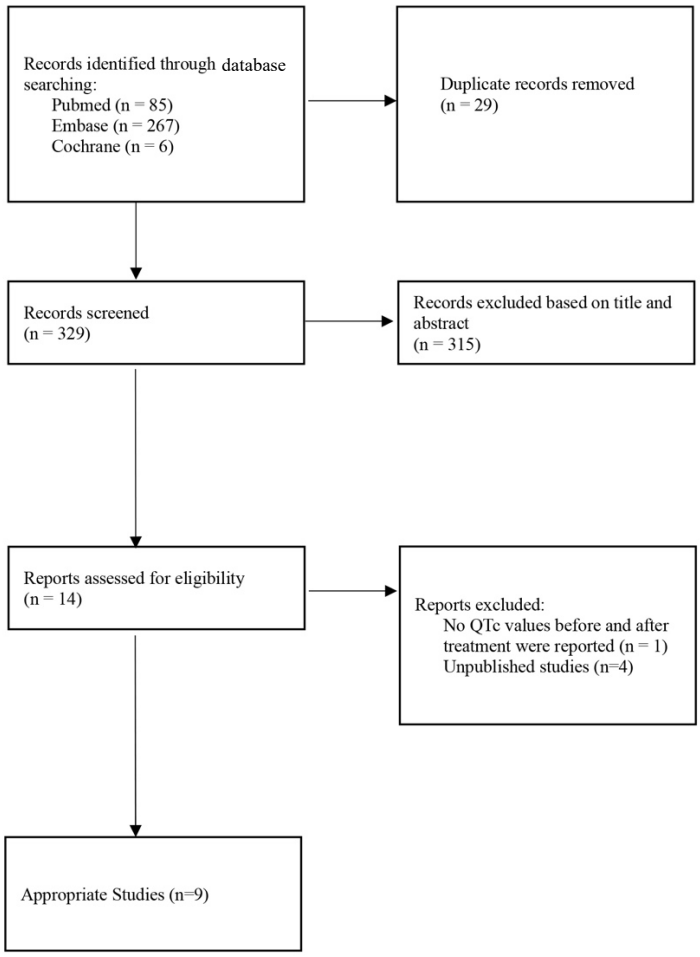


Figure 1. Flow diagram of literature searching.

Long QT patients with high-risk QTc significantly decreased to 21 (28%) patients (Risk Ratio [RR], 0.38; 95% CI 0.26-0.55; p<0.001) (Figure 2C).

Of the five studies[9-12,14] (n = 141) that included cardiac event reports, 48 (34%) patients had cardiac events before mexiletine treatment. The number of events was significantly reduced to 11 (7%) patients after mexiletine treatment (RR, 0.25; 95% CI 0.14-0.44; p<0.001) (Figure 2C).

Two studies reported side effects of mexiletine treatment.[10,14] One study[14] reported that 4 patients (33.3%) experienced gastrointestinal discomfort. Another study[10] reported 7 patients (22%) on the oral drug test had minor symptoms such as heartburn, nausea, vertigo, and epigastric pain, while 8 patients (9%) on chronic treatment experienced heartburn or nausea (In 4 cases, symptoms resolved simply by taking the treatment after meals and in the evening; in 4 other cases, therapy was suspended).

Table 1. Study characteristic and quality analysis.

Author, year of study	Study Design	Population Size	LQT subtype	Male/ female	Age (years)	Mexiletine Dosage and Route	Other treatment	Follow-up	Study Quality (NIH Quality assessment tools/NOS)
Bos J.M., et al (2019)[14]	Retrospective cohort study	12	LQT2; LQT 1 and 2; LQT 2 and 3	7/5	37.17 ± 25.5	4 to 6 mg/kg per dose/8 hours, oral	Beta-blocker 100%; LCSD 33%; ICD 8%	1.3 ± 0.9 years	Good/Good
Mazzanti A, et al (2016)[11]	Retrospective cohort study	34	LQT3	19/15	24.67 ± 27.86	average daily dose of 8 ± 0.5 mg/kg, oral	Beta-blocker 62%	59 months	Good/Good
Funasako M, et al (2016)[15]	**Prospective interventional cohort study**	31	LQT1; LQT2; LQT3	12/19	29 ± 18	2mg/kg, IV	NA	5 minutes after infusion	Good/Good
Ruan, et al (2007)[12]	**Prospective interventional cohort study**	5	LQT3	N/A	9.15 ± 6.15	6-8mg/kg/day, oral	Beta-blocker 100%	4.6 years	Good/Good
Schwartz P.J., et al (1995)[16]	**Prospective interventional cohort study**	15	LQT2; LQT3	6/9	20 ± 12	10 patients acute oral mexiletine 6 to 8 mg/ kg; 3 patients chronic oral mexiletine 12-16mg/kg/day, 1 patient acute and chronic therapy	Beta-blocker 47%; LCSD 40%; Pacemaker 13%	3 hours	Good/Good
Marwan B, et al (2015)[9]	**Prospective interventional cohort study**	12	aLQT	4/8	68 ± 10.14	Mexiletine (150 to 450 mg/day, oral	All patients receive TdP conventional treatment	2 hours	Good/Good
Dusi V, et al (2024)[17]	**Prospective interventional cohort study**	63	LQT1; LQT2; LQT3	N/A	N/A	N/A	Beta-blocker 100%	N/A	Fair/Poor
Blaufox A.D, et al (2012)[13]	Retrospective cohort study	13	LQT3	N/A	7.6 ± 5.9	7 mg/kg/day	N/A	1.2 years	Fair/Good
Crotti L, et al (2024)[10]	Retrospective cohort study	96	LQT2	45/53	16 ± 14	Acute oral drug test: 6 to 8 mg/ Kg; chronic oral therapy 9 ± 4 mg/kg	Beta-blocker 98%; LCSD 31%; ICD 29%	54 months	Good/Good

The quality of the studies was evaluated using the NIH Study Quality Assessment Tools and Newcastle-Ottawa Scale. ICD, implantable cardioverter-defibrillator; IV, intravenous; LCSD, Left Cardiac Sympathetic Denervation; N/A, Not Available; TdP, Torsade de Pointes.

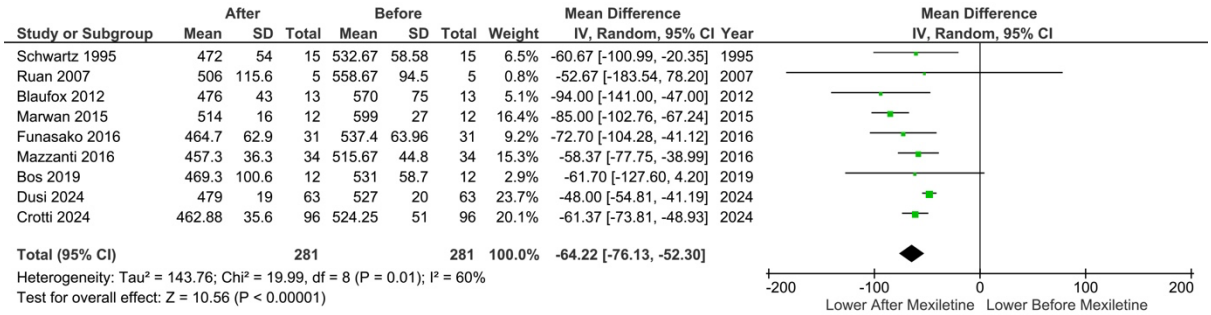
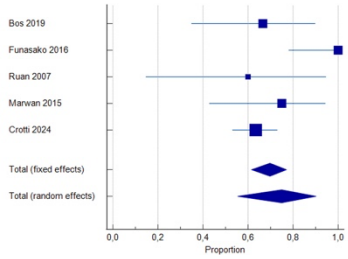


Figure 2A. MD with 95% CI of QTc reduction after mexiletine treatment.



Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Bos 2019	12	66,667	34,888 to 90,075	8,97	19,25
Funasako 2016	15	100,000	78,198 to 100,000	11,03	20,54
Ruan 2007	5	60,000	14,663 to 94,726	4,14	13,85
Marwan 2015	12	75,000	42,814 to 94,514	8,97	19,25
Crotti 2024	96	63,542	53,094 to 73,130	66,90	27,11
Total (fixed effects)	140	69,717	61,543 to 77,065	100,00	100,00
Total (random effects)	140	74,888	55,423 to 90,180	100,00	100,00

Figure 2B. Proportion of mexiletine responders with QTc reduction ≥40 ms.

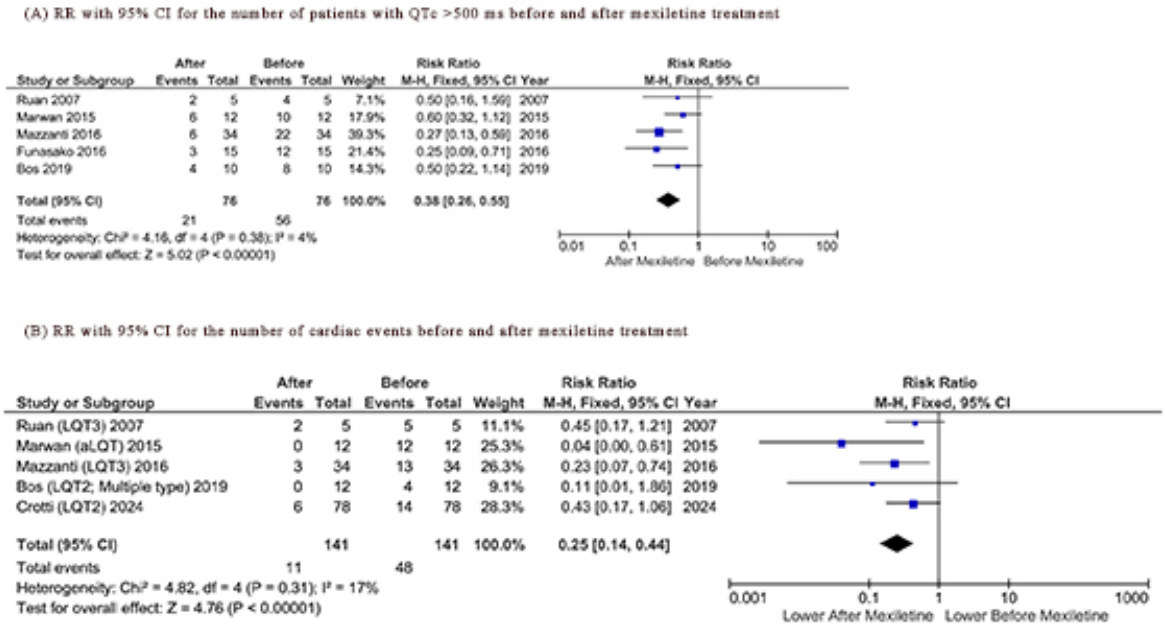


Figure 2C. (A) RR with 95% CI for the number of patients with QTc >500 ms before and after mexiletine treatment. (B) RR with 95% CI for the number of cardiac events before and after mexiletine treatment.

Effect on Different Subtypes of LQT

The heterogeneity in the main forest plot was moderate (60%), and a sub-analysis was needed to confirm the results for each subtype. There were 3 studies[10,14,16] that included the LQT2 population (n = 113). Mexiletine reduced QTc in the LQT2 population by approximately 60.2 ms (MD -60.22; 95% CI -72.05 to -48.38; p<0.001) (Figure 3). Five studies[11-13,15-16] included the LQT3 population (n = 75), with a QTc reduction of approximately 73 ms (MD, -72.64; 95% CI -87.31 − -57.98; p<0.001) after mexiletine treatment (Figure 3).

One study evaluated the aLQT, which was caused by stress-induced cardiomyopathy in 2 patients (16.7%), amiodarone in 5 patients (41.7%), levofloxacin in 2 patients (16.7%), dofetilide in 4

patients (33.3%), severe hypothyroidism in 1 patient (8.3%), and unidentified in 1 patient (8.3%).[9] Mexiletine reduced QTc in the aLQT population by approximately 85 ms (MD, -85.00; 95% CI -102.76 to -67.24; p<0.001).

There was no designated study focused only on the LQT1 population. Studies for rarer types of LQT were still limited to be included and evaluated in this meta-analysis.

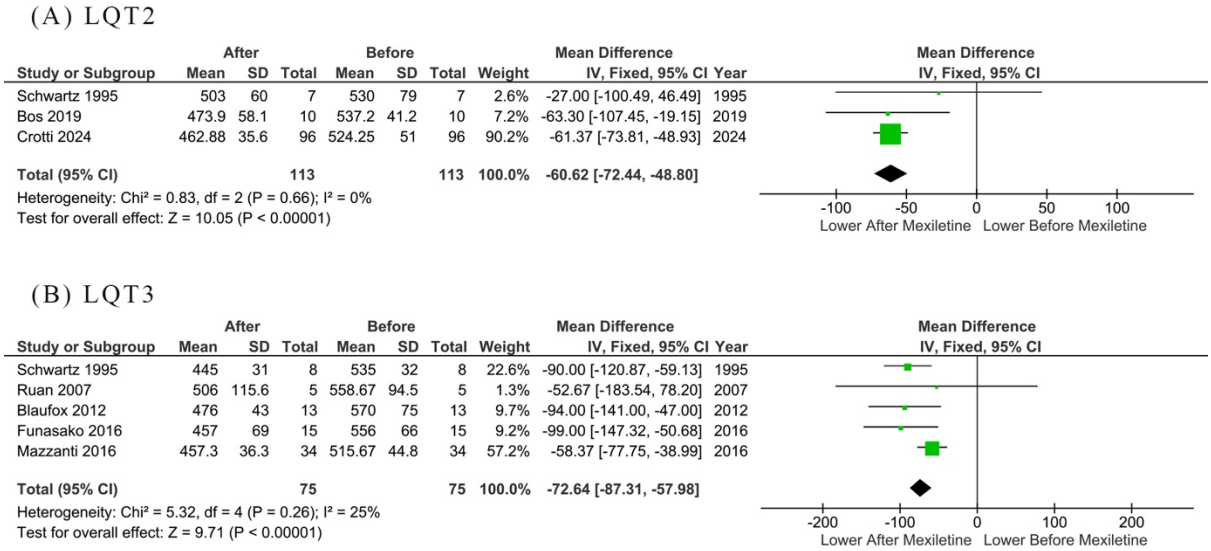


Figure 3. Forest Plot MD with 95% CI for each LQT type. (A) LQT2; (B) LQT3.

Discussion

The primary finding of this meta-analysis was that mexiletine significantly reduced QTc in LQT2, LQT3, and aLQT. Although the study showed moderate heterogeneity, the sub-analysis of each type of LQT indicated that mexiletine was able to reduce QTc significantly. The sensitivity analysis revealed that the removal of outliers reduced the heterogeneity from $I^2 = 60\%$ to $I^2 = 0\%$, indicating that these studies contributed substantially to the variability in the original analysis. These results confirm the robustness of our findings, supporting the efficacy of mexiletine in reducing QTc across LQT2, LQT3, and aLQT populations, with more consistent effects across studies. One study[17] was identified as an outlier and excluded from the final analysis due to concerns about the quality of the data, as the study did not provide adequate details. These limitations raise concerns about the reliability and accuracy of its findings.

Mexiletine works as a sodium channel blocker (Class Ib) that can reduce the prolonged sodium current (INa-L), as observed in LQT3 (a gain-of-function mutation in the SCN5A gene). The gating state of sodium channels may also be regulated by interactions among cardiac ion channels, which can be abnormal in conditions like LQT1 (Iks) and LQT2 (Ikr).[18-19] Mexiletine also reduces the action potential duration (APD) in cardiac myocytes by inhibiting the inward sodium current, which shortens the overall QTc and can benefit patients with LQT1, LQT2 and possibly other types of LQT.[19-20] The QTc reduction may occur due to the multi-hit model and the phenomenon of repolarization reserve, which suggests that repolarization is not regulated by only a single ion channel.[21-22] A similar result was shown in human-induced pluripotent stem cells from patients with LQT2, as well as in cardiomyocytes isolated from LQT2 rabbits (shortening the APD by 113 ms).[10] Mexiletine's efficacy was also demonstrated in patients with aLQT, which is primarily caused by the abnormality of potassium and sodium channels.[19,23-24] A study[24] reported on the efficacy of mexiletine in patients who were administered dofetilide. These results are similar to our meta-analysis (which also included a broader range of etiologies). One of the studies included in this meta-analysis reduced the risk of bias in aLQT management by administering mexiletine only after conventional treatments—especially the removal of the cause—were deemed ineffective, as evidenced by refractory torsade de pointes (TdP). The gene mutation is also suspected to be a risk factor in aLQT patients but has only been reported in a minority of cases.[5,25] The time-to-onset of aLQT may vary among drugs, which can affect the

timing of treatment withdrawal, making it difficult to prevent TdP and increasing the reliance on curative treatment.[26]

Mexiletine caused only slight changes in hemodynamic variables without significantly affecting the left ventricular systolic or diastolic function, resulting in a low incidence of significant side effects. This makes mexiletine a safer option for bradycardia-induced QT interval prolongation, as beta-blockers can worsen the condition.[19,23] Compared to other Class Ib drugs, mexiletine is more effective in treating LQTS patients.[8] Two studies[10,14] from this meta-analysis reported gastrointestinal (GI) problems and vertigo as side effects of mexiletine treatment. While mexiletine is generally considered safe, some patients experienced symptoms that required therapy suspension, indicating that further research on its safety profile is still needed.[10]

In this meta-analysis, 56 (73%) patients had QTc >500 ms (including LQT2, LQT3 and aLQT), which can increase both short- and long-term mortality.[1,27] Achieving a reduction in QTc is important, but reducing it to below 500 ms is crucial. In this study, 23 patients (30%) achieved this reduction (RR 0.45). In this meta-analysis, mexiletine was found to reduce the number of cardiac events. Similar results have been reported in patients with PVC or even in patients with recurrent VT/VF, which are refractory to other types of antiarrhythmics.[23,28] Based on ESC guidelines, so far, mexiletine is currently indicated only for LQT3 patients (Class I, Level of Evidence C recommendation).[19,29] This meta-analysis provides evidence to support the use of mexiletine for LQT2 and aLQT, and it is hoped that it will inspire further research into its use for other types of LQTS.

Limitation

The limitations of this meta-analysis are as follows: (1) The limited population size and number of studies hindered more detailed analyses, such as evaluating the effectiveness of mexiletine therapy in less common LQTS subtypes or assessing potential confounding factors influencing its therapeutic efficacy; (2) Further research with standardized dosing, therapeutic combinations, and routes of administration is required to provide stronger evidence regarding the effectiveness and safety profile of mexiletine therapy.

Conclusion

This meta-analysis concluded that mexiletine significantly reduced QTc and cardiac events in patients with LQT2, LQT3, and aLQT. Mexiletine also significantly reduced the number of Long QT patients with high-risk QTc. These findings support the use of mexiletine for LQT2 and aLQT and encourage further research into other LQTS types.

List of Abbreviations

aLQT	Acquired Long QT Syndrome
APD	Action Potential Duration
CI	Confidence Interval
ESC	European Society of Cardiology
GI	Gastrointestinal
ICD	Implantable Cardioverter Defibrillator
INa-L	Late Sodium Current
IQR	Interquartile Range
IV	Intravenous
LCSD	Left Cardiac Sympathetic Denervation
LQT1	Long QT Syndrome Type 1
LQT2	Long QT Syndrome Type 2
LQT3	Long QT Syndrome Type 3
LQTS	Long QT Syndrome
MD	Mean Difference
NIH	National Institutes of Health
NOS	Newcastle-Ottawa Scale
ORCID	Open Researcher and Contributor ID
PRISMA	Preferred Reporting Items of Systematic Reviews and Meta-Analyses
QTc	Corrected QT Interval
RR	Risk Ratio
TdP	Torsade de Pointes

Ethical Clearance

No new human participants or subjects were involved in this study (this meta-analysis used previously published data).

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

DIR – Conceptualization, Methodology, Formal analysis, Data collection, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Literature search, Software, Visualization.

MIQ – Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.

CJC – Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.
CA – Formal analysis, Investigation, Writing - Review & Editing, Supervision
MP – Formal analysis, Investigation, Writing - Review & Editing, Supervision
HSP – Formal analysis, Investigation, Writing - Review & Editing, Supervision.
MRA – Methodology, Writing - Review & Editing, Supervision.

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None.

Conflict of Interest
The authors declare that they have no conflicts of interest.

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.
The software/code used in this study is available from the corresponding author upon reasonable request.

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Case Report

Hemodynamic impairment of double culprit ST elevation myocardial infarction, double the trouble: a case report

Mikhael Asaf[1], Jonathan Edbert Afandy[2], Siska Suridanda Danny[3]

Abstract

Background: Multiple culprit artery involvement is rare (2.5%) among ST-segment elevation myocardial infarction (STEMI) patients undergoing primary coronary intervention (PCI). It can occur due to multiple factors and reflects a widespread pathophysiologic process. Most patients present with unstable hemodynamics and cardiogenic shock (CS), which results in a high mortality rate. Currently, there are no guidelines or consensus on the management of multiple culprit arteries in STEMI patients.

Case Illustration: A 51-year-old man with chest pain for the past 16 hours was referred to the National Cardiovascular Center, Harapan Kita. ECG at presentation revealed sinus rhythm with ST elevation in the inferior, posterior, and right leads. He was diagnosed with late-onset infero-posterior STEMI + right ventricle infarction, Killip IV, and thrombolysis in myocardial infarction 6/14, then was prepared for early PCI due to ongoing chest pain and CS. The patient underwent complete revascularization with drug-eluting stents and thrombus aspiration due to the high thrombus burden of the lesion in the right coronary artery and first obtuse marginal artery. After early PCI, his hemodynamic condition improved, and epigastric pain was his only complaint. However, on the following day, the patient experienced acute pulmonary edema and rhythm conversion to total AV block. He was managed conservatively with heparinization, inotropes, vasopressors, diuretics, and noninvasive ventilation. After 14 days of hospitalization, the patient was discharged without any complaints.

Conclusion: Double culprit STEMI is rare and associated with catastrophic hemodynamic impairment, including CS, at presentation. Individualized treatment with early and aggressive revascularization yields relatively good results.

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Keywords: *double culprit, STEMI, total AV block, cardiogenic shock, case report.*

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Introduction

In cases of acute ST-segment elevation myocardial infarction (STEMI), usually, only one epicardial coronary artery is completely occluded by thrombus, referred to as the "culprit" artery, and the rate of having multiple culprit arteries is only 2.5% among patients undergoing emergent primary percutaneous coronary intervention (PCI).[1] In contrast, from an autopsy series, it was found that multiple culprit artery thrombotic occlusions occurred in up to 50% of patients.[2] This discrepancy may be explained by the fact that patients with multiple culprit STEMI are more likely to experience sudden cardiac death and not survive long enough to undergo angiography.

Multiple acute coronary thromboses can occur due to multiple factors, including plaque rupture, erosion, coronary artery dissection, coronary vasospasm, cocaine abuse, hypercoagulability, or coronary embolism; however, in most cases, the underlying mechanisms remain unclear.[3] At least in some cases, acute coronary events reflect widespread pathophysiologic processes, which may lead to multifocal plaque instability coupled with clinical instability at multiple locations.[4] One certain thing is that multiple culprit STEMI cases are related to unstable hemodynamics and cardiogenic shock (CS), which results in a high mortality rate.[1-2]

Currently, there are no guidelines or consensus on the management of multiple culprit arteries in STEMI patients. This case report aims to present the hemodynamic impairment of a patient with late-onset STEMI who presented with simultaneous total occlusion of two major epicardial coronary arteries treated with immediate complete revascularization.

Case Illustration

A 51-year-old male was referred to the National Cardiovascular Center Harapan Kita emergency department with a complaint of chest pain accompanied by nausea and sweating in the past 16 hours. The patient had a history of uncontrolled hypertension and was a smoker. He was referred with a diagnosis of inferior STEMI (Figure 1) complicated by CS and total AV block (TAVB) and had received 320 mg aspirin, 300 mg clopidogrel, 5000 IU heparin continued with 1000 IU/24 hours, 40 mg atorvastatin, and hemodynamic support using dobutamine, dopamine, and norepinephrine.

Upon arrival at our hospital, his blood pressure was 88/61 mmHg, and his heart rate was 110 beats per minute (bpm) with support of dobutamine 7 mcg/kg/min, dopamine 5 mcg/kg/min, and norepinephrine 0.05 mcg/kg/min. His lung sounds were vesicular with bilateral 1/3 basal rales. ECG at 16 hours after onset revealed sinus tachycardia with a rate of 107 bpm, left axis deviation, a normal P wave, a PR interval of 160 ms, pathological Q waves in II, III, avF, V3R-V4R, and V7-V9, a QRS duration of 90 ms, ST elevation in III, avF, and V8-V9, ST depression in I, avL, and V2-V4, and left ventricle hypertrophy (Figure 2). Laboratory tests revealed reduced renal function (urea 42 mg/dL, creatinine 2.37 mg/dL, eGFR 33 mg/mmol) and elevated high-sensitivity troponin T (4314 ng/mL). Bedside echocardiography revealed a reduced left ventricular ejection fraction (LVEF) (18%), reduced tricuspid annular plane systolic excursion (TAPSE) (7 mm), and regional wall motion abnormalities seen as akinetic inferolateral and inferior segments, while other segments were hypokinetic. His hemodynamics profiles were elevated estimated right atrial pressure (15 mmHg), low cardiac output (CO) (1.6 L/min), and high systemic vascular resistance (SVR) (3150 dynes/sec/cm^{-5}). He was then diagnosed with late-onset (16 hours) inferoposterior STEMI + right ventricle infarction, Killip IV, and thrombolysis in myocardial infarction (TIMI) 6/14, with acute kidney injury dd/acute on chronic kidney disease. The patient was then prepared for early PCI. Dopamine was stopped, dobutamine was increased to 10 mcg/kg/min, and another loading of 300 mg of clopidogrel was given.

Coronary angiography during early PCI revealed total occlusion of the proximal right coronary artery (RCA) (Figure 3A) and proximal first obtuse marginal artery (OM1) (Figure 3B) with thrombus grade V and TIMI 0 flow. Balloon predilatation and thrombus aspiration were initially performed at the RCA. A 3.5x33 mm Xience Xpedition (Abbott Vascular, USA) drug-eluting stent (DES) was implanted, and the final angiographic evaluation of the RCA revealed TIMI 3 flow with no residual thrombus or stenosis and no perforation (Figure 3C). For the OM1 lesion, balloon predilatation was performed initially, followed by stent implantation with a 2.5x20 mm Promus Premiere (Boston Scientific, USA). Because the angiographic evaluation showed TIMI 2 flow with a hazy appearance, it was decided to perform thrombus aspiration once, which resulted in TIMI 3 flow with residual thrombus, no residual stenosis, and no perforation (Figure 3D). The patient is then transferred to the intensive cardiovascular care unit (ICVCU).

After the procedure, the patient experienced no more chest pain but epigastric pain with a VAS score of 2/10. Hemodynamic echocardiography revealed improvement with dobutamine 5 mcg/kg/min as the patient's only hemodynamic support. However, one day after the early PCI, the patient experienced respiratory distress with signs of acute pulmonary edema and reduced SpO_2 to 92-93% on 3 3-liter per minute nasal cannula. His ECG changed to TAVB with a junctional escape rhythm, and his heart rate decreased from 110-120 to 80-90 bpm without any sign of new ischemic changes (Figure 4). Hemodynamic echocardiography revealed reduced CO from 3.8 to 2.6 L/min and increased SVR from 1410 to 1907 dynes/sec/cm^{-5}. His laboratory test also revealed worsening renal function due to hypoperfusion (creatinine 3.0 mg/dL).

For the TAVB, 5 mcg/kg/min dopamine was added, and his heart rate increased from 80 to 100 bpm. His hemodynamics also improved, with CO increasing to 3.5 L/min and SVR to 1440 dynes/sec/cm-5. For breathing problems, oxygen supplementation was escalated to noninvasive ventilation (NIV) with 5 mmHg positive end-expiratory pressure, 5 mmHg pressure support, and 70% FiO_2. His blood gas analysis showed improvement (lactate decreased from 3.4 mg/dL to 2.0 mg/dL), and his SpO_2 increased to 99%. A bolus of 40 mg intravenous furosemide was also administered and continued at 5 mg/hour. Heparinization with UFH continued until 5 days after early PCI. His urine output target (1.5 cc/kg/hour) was achieved the next morning, and his creatinine level improved to 1.8 mg/dL.

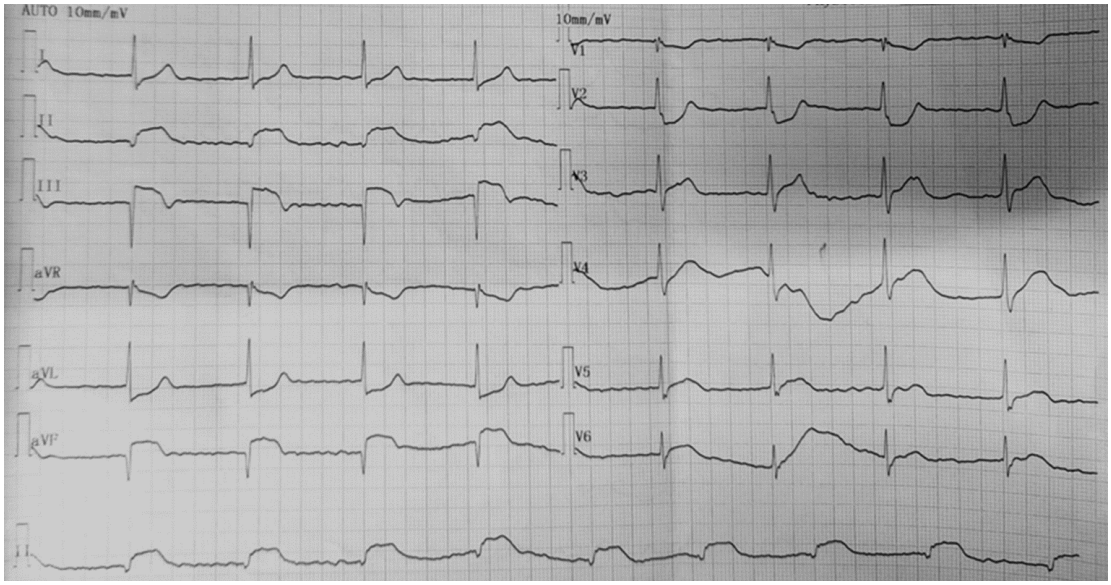

Figure 1. ECG at 5 hours after onset.
Total AV block with atrial fibrillation, inferior leads ST-Elevation.

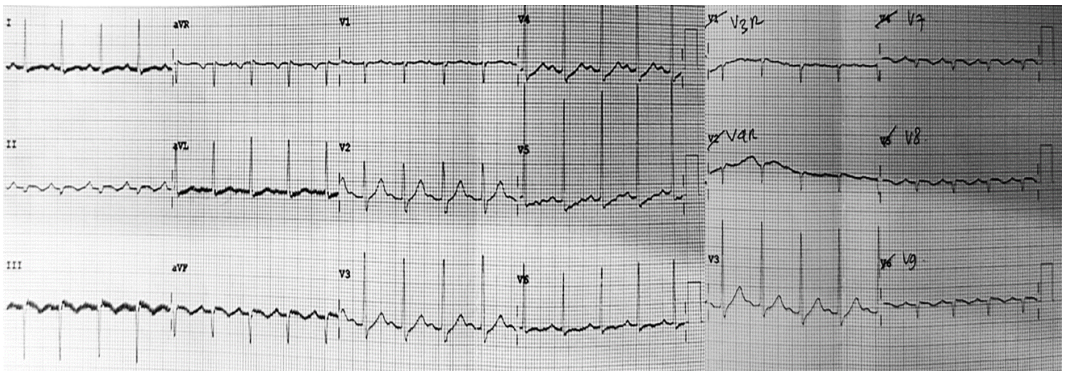

Figure 2. ECG at 16 hours after onset.
Sinus tachycardia with inferoposterior and right leads ST-Elevation.

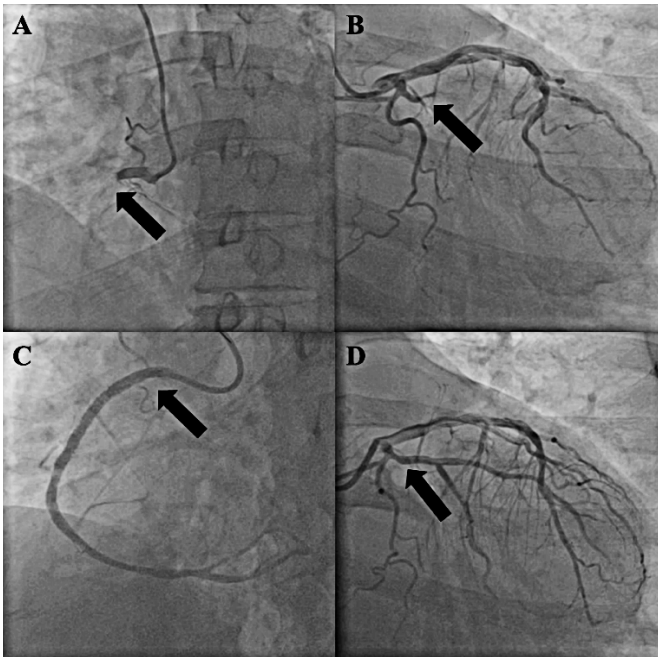

Figure 3. Early percutaneous coronary intervention.
Initial angiography showing lesions in A) right coronary artery and B) first obtuse marginal artery; final angiography of C) right coronary artery and D) first obtuse marginal artery.

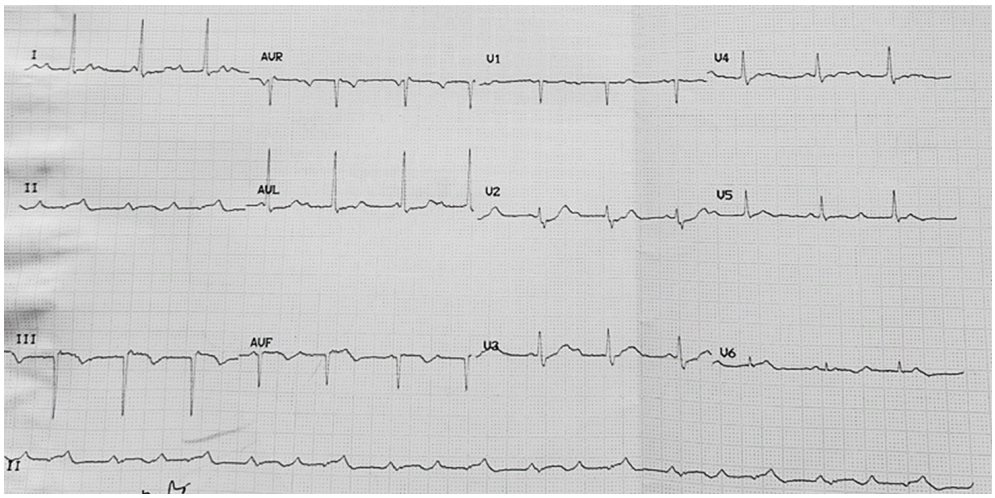

Figure 4. ECG one day after early percutaneous coronary intervention.
TAVB with accelerated junctional escape rhythm, no new ischemic changes.

After 7 days in the ICVCU, his rhythm returned to sinus, and after 10 days, he was able to weaned from all support and moved to the general ward. His medication was changed to oral medication, and after 14 days of hospitalization, he was discharged without any complaints with medication of 1x80 mg aspirin, 2x90 mg ticagrelor, 1x20 mg atorvastatin, 1x0.6125 mg bisoprolol, 1x10 mg ramipril, 1x25 mg spironolactone, and 2x40 mg furosemide. Predischarge echocardiography showed improvement in his LVEF (42%) and TAPSE (18 mm). Summary of the case timeline presented in Figure 5.

Discussion

The term culprit lesion refers to the coronary lesion considered to be responsible for Acute Coronary Syndrome (ACS). According to the 2020 European Society of Cardiology (ESC) guidelines on ACS presenting without ST-segment elevation, at least two of the following morphological features suggestive of acute plaque rupture should be present: (1) intraluminal filling defects consistent with thrombi; (2) plaque ulceration; and (3) plaque irregularity, dissection, or impaired flow.[5] In our patient, we observed intraluminal filling defects consistent with thrombi showing

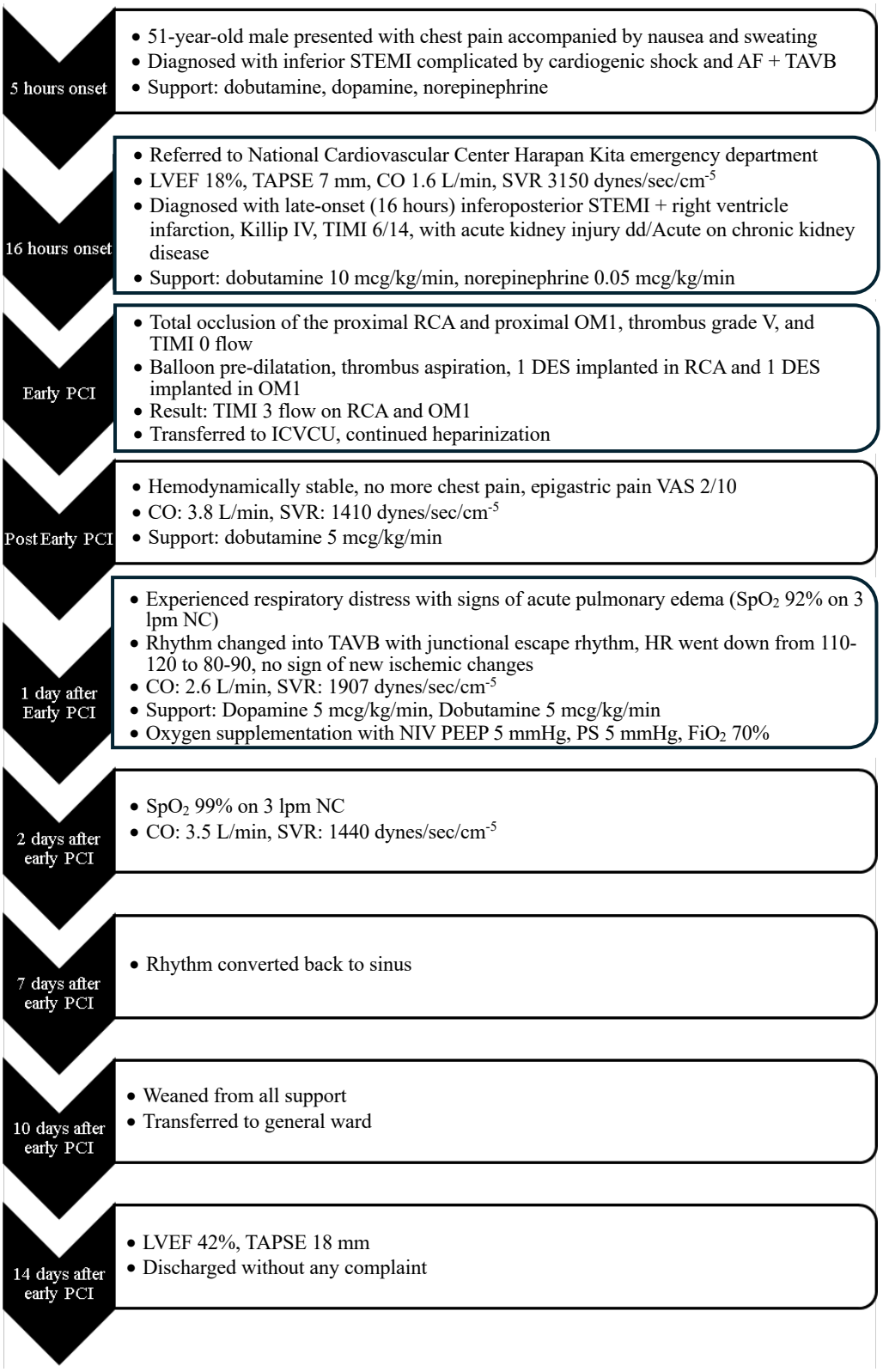

Figure 5. Case timeline.

STEMI: ST-elevation myocardial infarction; AF: atrial fibrillation; TAVB: total AV bock; LVEF: left ventricle ejection fraction; TAPSE: tricuspid annular plane systolic excursion; CO: cardiac output; SVR: systemic vascular resistance; TIMI: thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; OM1: first obtuse marginal artery; DES: drug-eluting stent; ICVCU: intensive cardiovascular care unit; NC: nasal cannula; HR: heart rate; NIV: non-invasive ventilation; PEEP: positive end-expiratory pressure; PS: pressure support.

acute occlusion abruptly ending with a squared-off or convex margin with impaired flow in two major epicardial coronary arteries, the RCA and OM1. Furthermore, contrast staining consistent with the TIMI thrombus burden classification was also observed for OM1. We can also note that after PCI, angiography of the RCA revealed no collaterals to the LCx, which confirmed that the occlusion was of acute origin. Therefore, it is concluded that the patient had a double culprit lesion.

A systematic review by Mahmoud et al.[2] on simultaneous multivessel coronary thrombosis in patients with STEMI found that the mean age of the patients was 59 years; most were male (88%), were current smokers (59%), and had a history of hypertension (50%). Atrial fibrillation (AF) at presentation or a history of AF was not common (5%). CS was the most common clinical presentation, occurring in 41% of the patients, followed by ventricular arrhythmias (25%). The most common territory of ST-segment elevation seen on ECG is in the inferior leads (29%). Meanwhile, from coronary angiography findings, the most common coronary artery with a thrombus burden was the RCA + left anterior descending artery (50%), followed by the RCA + left circumflex artery (LCx) (32%). Our patient had similar clinical characteristics to those reported in the literature. He was a male with a history of uncontrolled hypertension and was a current smoker. He presented with CS and ST elevation in the inferior leads. His coronary angiography result was the second most common finding, which involved the RCA + LCx.

Currently, there are no guidelines or consensus on the management of multiple culprit arteries in STEMI patients. The available guidelines or trials are limited to patients with multivessel disease (MVD) who present with ACS and are related to the decision on when to revascularize another significant non-Infarct-Related Artery (IRA) stenoses. Nevertheless, complete revascularization is recommended for STEMI patients with MVD either during the index procedure or within 45 days due to better mortality outcomes.[6] For patients presenting with STEMI and CS, according to the SHOCK[7] and CULPRIT-SHOCK[8] trials, immediate revascularization of the IRA only was advised. Table 1 provides insight into several case reports showing different interventions for double culprit STEMI. However, due to the large territory of the myocardium jeopardized by double culprit STEMI, all reports have shown early and aggressive attempts at complete revascularization that yielded relatively good results.

Our patient arrived on late-onset (16 hours) compared to other case reports (<6 hours) and beyond the ideal time frame for primary PCI (<12 hours).[15] However, due to the presence of CS and ongoing chest pain, our patient was scheduled for early PCI. We decided to perform complete revascularization because both lesions were deemed to be culprit lesions. Thrombus aspiration was performed because, after predilation in the RCA and placement of the stent in the LCx, there was still residual thrombus. Although the TOTAL[16] trial revealed that routine thrombus aspiration did not improve outcomes and was associated with an increased rate of stroke in patients with a high thrombus burden, current ESC guidelines on ACS still recommend it in patients with a large residual thrombus burden after opening the vessel with a guide wire or balloon.[15] Anticoagulants should generally be discontinued immediately after PCI, except in specific clinical circumstances.[15] However, in our case, the patient was still given heparinization for 5 days because there was still a hazy appearance in the acute marginal branch and OM1 according to angiography. We found that the patient's clinical condition (epigastric pain) and rhythm were also improved after heparinization, which was consistent with the observed improvement in ischemia. After heparinization, the patient's P2Y12 inhibitor was also escalated from clopidogrel to ticagrelor.

Because the patient's condition deteriorated due to rate problems, we decided to administer dopamine for his TAVB. However, it was decided not to rush the use of a temporary pacemaker because the escape QRS complex was still narrow, suggesting a supra-Hisian block that might respond to medication.[17] Meanwhile for the use of mechanical circulatory support, we planned to use an intra-aortic balloon pump (IABP) because although there was significant improvement in our patient's hemodynamics with dopamine, his CO (from 2.6 to 3.5 L/min) and SVR (from 1907 to 1440 dynes/sec/cm^{-5}) still exhibited borderline values, with a cardiac index of 1.9 L/min/m^2. Nevertheless, the current guidelines from the IABP-SHOCK II study do not suggest the routine use of the IABP in patients without mechanical complications due to the lack of improvement in mortality.[15,18] In the end, we only used inotropic/vasopressor drugs, and fortunately, our patient responded well.

Table 1. Various case reports on double culprit STEMI

Author	Onset	Intervention	Outcome
Hage et al.[9]	3 hours	• GP IIb/IIIa • Thrombus aspiration (LAD and RCA) • LMWH (4 days)	The patient was discharged on day 5, with decreasing troponin, normal kidney function, and no hemorrhagic complications. OCT evaluation → thrombus (-)
Turgeman et al.[10]	3 hours	• IABP • GP IIb/IIIa • Thrombus aspiration + 125,000 units of urokinase (LAD and RCA)	Seven days post-admission, repeat coronary angiography showed near-normal coronary vessels
Caliskan et al.[11]	No data	• PCI of RCA and LAD	Resolution of chest pain, ST-elevation, and hemodynamic stabilization
Saito et al.[12]	40 mins	• TAVB → TPM • Thrombus aspiration → DES (RCA and LAD) • Impella CP (3 days)	On the 12th day, the patient had a stroke → discharged on the 57th day of hospitalization with NYHA class II HF
Nordkin et al.[13]	1.5 hours	• PCI of LCx and RCA	On day six, the patient was discharged in good medical condition without signs of congestive heart failure (CHF).
Ginanjar et al.[14]	2 hours	• Thrombus aspiration and DES in LAD and LCx	Improvement of patient clinical condition, ST elevation, and hemodynamic status

Conclusion

A rare case of double culprit STEMI has been presented. It is usually associated with catastrophic hemodynamic impairment, including CS at presentation, due to a large area of myocardium being jeopardized. The underlying mechanism in most patients remains unclear, with no specific guidelines or consensus on its management. However, individualized treatment with early and aggressive revascularization yields relatively good results.

List of Abbreviations

AF Atrial Fibrillation
CO Cardiac Output
CS Cardiogenic Shock
DES Drug-eluting Stent
ECG Electrocardiogram
HR Heart Rate
ICVCU Intensive Cardiovascular Care Unit
LVEF Left Ventricle Ejection Fraction
NC Nasal Cannula
NIV Non-invasive Ventilation
OM1 First Obtuse Marginal Artery
PCI Primary Percutaneous Coronary Intervention
PEEP Positive End-expiratory Pressure
PS Pressure Support
RCA Right Coronary Artery
STEMI ST-segment Elevation Myocardial Infarction
SVR Systemic Vascular Resistance
TAPSE Tricuspid Annular Plane Systolic Excursion
TAVB Total AV Block
TIMI Thrombolysis in Myocardial Infarction
UFH Unfractionated Heparin
VAS Visual Analogue Scale

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors' Contributions

MA: Conception, case management, data collection, drafting, and critical revision of the manuscript; JEA: Case management support, literature review, drafting of clinical details, and

manuscript editing; SSD: Senior supervision, critical revision of intellectual content, and final approval of the version to be published.

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Conflict of Interest
The authors declared that they have no competing interests.

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Case Report

Hemodynamic Conundrum of Thyroid Storm-Induced Acute Heart Failure: Challenging Case in a Remote Area

Dya Pratama Andryan[1], Susandy Oetama[2], Oktavia Lilyasari[3]

Abstract

Background: Thyroid storm (TS) is an acute and critical presentation of hyperthyroidism. It can lead to multiple organ dysfunction and has a high rate of mortality. Heart failure is one of the grave complications of hyperthyroidism and thyroid storm. Rapid progression of TS can lead to hypoperfusion and shock even with normotensive blood pressure and normal hemodynamic parameters. Unfortunately, the prevalence of hyperthyroidism is high in developing areas that lack of advanced medical facilities. This case presentation aims to present the rare condition of acute high-output failure secondary to thyroid storm with hypoperfusion and normotensive shock.

Case Illustration: A 28-year-old man came to the emergency department of a private hospital in East Borneo with worsening dyspnea on effort for three days before admission. His blood pressure was 169/103 mmHg with an irregular heart rate at 135-148 bpm. His axillary temperature was 37.9°C. ECG showed rapid Atrial Fibrillation (AF) with Ashman phenomenon. Chest x-ray revealed cardiomegaly with flattened cardiac waist and lung infiltrate. His echocardiogram has a hyperdynamic LV with LVEF 70%, normal RV function, concentric LV hypertrophy, and increased LAVi (51.19 mL/m^2). From the initial echocardiogram hemodynamic assessment, eRAP was 15 mmHg, CO was 6.5 to 7.4 L/min, and SVR was 1167 to 1329 dyne/sec/cm^{-5}. His peak E wave velocity was 92-95 cm/s. His fT4 was increased (100 ng/dL) while TSH was reduced (0.007 mU/L). H2FPEF score estimated 38.7% probability of heart failure with preserved ejection fraction (HFpEF). Burch-Wartofsky score was 60, suggesting thyroid storm. He was diagnosed with acute high-output heart failure secondary to thyroid storm due to uncontrolled Graves' Disease, and AF with rapid ventricular response. During follow-up in the Intensive Care Unit (ICU), patients underwent hypoperfusion with normotensive blood pressure (normotensive shock). Norepinephrine was initiated. The patient kept deteriorating and then passed away in our critical care unit at day of the seventh day.

Conclusion: Thyroid storm-induced acute heart failure might have a conundrum presentation due to normotensive and good cardiac output, giving a false impression of hemodynamic condition. Clinical presentation was very important to identify hypoperfusion, and aggressive treatment was needed to stabilize the patient's condition.

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Keywords: *Acute heart failure, high output, thyroid storm, hyperthyroidism, hypoperfusion*

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Introduction

Thyroid storm (TS) is an acute and critical manifestation of hyperthyroidism.[1-2] It can lead to multiple organ dysfunction and has a high mortality rate. Heart failure is one of the grave complications associated with hyperthyroidism and TS. Thyroid-related heart failure is characterized by high-output heart failure, with uncompromised (and often increased) cardiac output; however, congestion occurs due to diastolic dysfunction and poor Left Ventricular (LV) filling secondary to tachyarrhythmia.[3-4] Rapid progression of TS can lead to hypoperfusion and shock, even with normotensive blood pressure and normal hemodynamic parameters. Unfortunately, hyperthyroidism has become increasingly prevalent in developing regions that lack advanced medical facilities.[1] Hence, this case presentation aims to illustrate the rare condition of acute high-output heart failure secondary to thyroid storm, accompanied by hypoperfusion and normotensive shock.

Case Illustration

A 28-year-old man was presented to the emergency department of a private hospital in East Borneo with worsening dyspnea three days before admission. He also reported palpitations, constant fever, and "air hunger" when lying flat. Additionally, he noticed swelling in both legs. His medical history indicated stage II hypertension, for which he was not taking his medication regularly; nevertheless, there were no other remarkable findings in his medical records. However, upon examination, his blood pressure was 169/103 mmHg, with an irregular heart rate of 135 bpm to 148 bpm. His axillary temperature was 37.9°C. Notable physical findings included alopecia areata, exophthalmos, icteric sclera (Figure 2B-C), an enlarged non-nodular thyroid gland measuring 2x1.5 cm^2, minimal rales at the bilateral lung bases, a faint systolic murmur at the lower sternal border and apex graded 3/6, and bilateral pitting oedema. Capillary refill time was over 2 seconds, with warm but clammy extremities. His ECG result revealed rapid atrial fibrillation with Ashman phenomenon (Figure 2A). A chest X-ray test showed cardiomegaly with a flattened cardiac waist and lung infiltrates. His echocardiogram indicated hyperdynamic LV function with an LVEF of 70%, normal RV function, concentric LV hypertrophy (Figure 2D-E), and increased Left Atrial Volume Index (LAVI) of 51.19 mL/m^2. The initial echocardiographic hemodynamic assessment demonstrated an estimated Right Atrial Pressure (eRAP) of 15 mmHg, Cardiac Output (CO) of 6.5 to 7.4 L/min, and Systemic Vascular Resistance (SVR) of 1167 to 1329 dyne/sec/cm^5. His peak E wave velocity was 92 - 95 cm/s (Figure 2F); however, due to limitations, we cannot measure Tissue Doppler Index (TDI) or calculate Pulmonary Arterial Wedge Pressure (PAWP). Additionally, abdominal ultrasound findings were consistent with a "starry sky" appearance, indicative of ischemic acute hepatitis. His free T4 (fT4) was increased (100 ng/dL), while TSH was suppressed (0.007 mU/L). The H2FPEF score estimated a 38.7% probability of Heart Failure with Preserved Ejection Fraction (HFpEF). The Burch-Wartofsky score was 60, suggesting a thyroid storm.

He was diagnosed with acute high-output heart failure secondary to a thyroid storm due to uncontrolled Graves' disease and rapid ventricular response, atrial fibrillation. For acute heart failure, he was treated with intravenous furosemide at 5 mg/hr, ramipril 5 mg once daily, hydrochlorothiazide (HCT) 25 mg once daily, and spironolactone 25 mg once daily. For his atrial fibrillation, he received warfarin 2 mg once daily, propranolol starting at 10 mg thrice daily, and digoxin IV 0.25 mg as needed. For his thyroid storm, he was treated with methimazole 20 mg four times daily and dexamethasone 2x5 mg IV. Unfortunately, Lugol's solution was unavailable. During his follow-up in the Intensive Care Unit (ICU), the patient showed improvement over the first two days, with reduced dyspnea, improved congestion profile, and stabilized blood pressure and heart rate. His urine output was 2 L to 3 L per day. However, on day three, the patient began to deteriorate. His blood pressure dropped to 116/45 mmHg without support, and his heart rate was 78 bpm, but his diuresis fell below <1 cc/kg/min. On day four, the patient developed metabolic acidosis, with blood gas analysis revealing a pH of 7.26, pCO_2 of 45.2 mmHg, pO_2 of 102 mmHg with nasal cannula at 3 L/min, and HCO_3^- of 21.7 with an actual base excess of -5.1. The patient's awareness and renal function deteriorated, prompting the discontinuation of medications affecting blood pressure and renal condition, such as ramipril, HCT, and spironolactone. Serial hemodynamic echocardiograms revealed an eRAP of 8 mmHg, CO of 3.9 – 4 L/min, and SVR of 1100–1128 dyne/sec/cm^5. We suspected this condition was due to hypoperfusion with normotensive blood pressure (normotensive shock). Subsequently, we initiated norepinephrine at 0.05 mcg/kg/min, titrated upwards, and corrected acidosis with IV bicarbonate. The patient continued to deteriorate and passed away in the critical care unit on the seventh day.

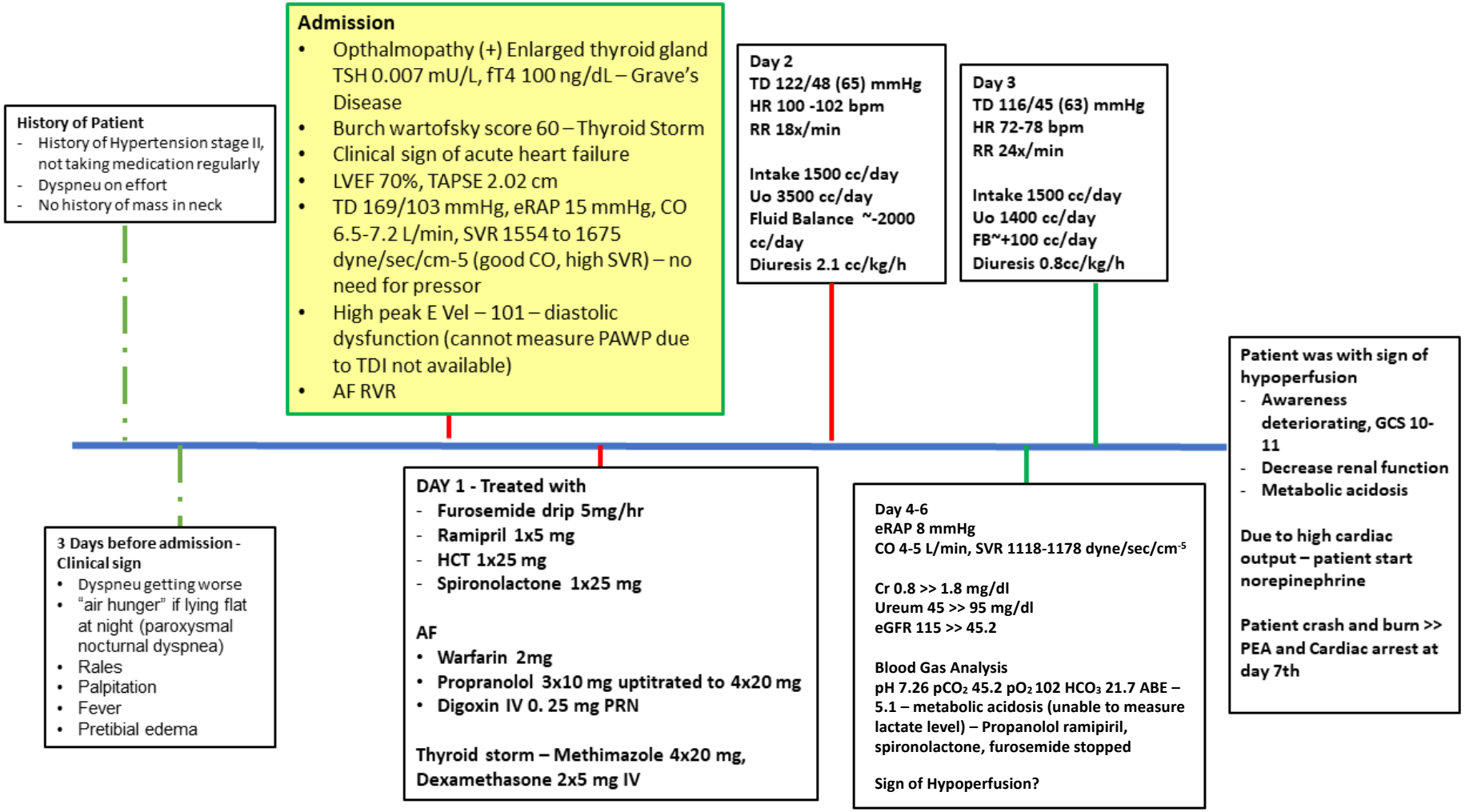

Figure 1. Timeline of the case.

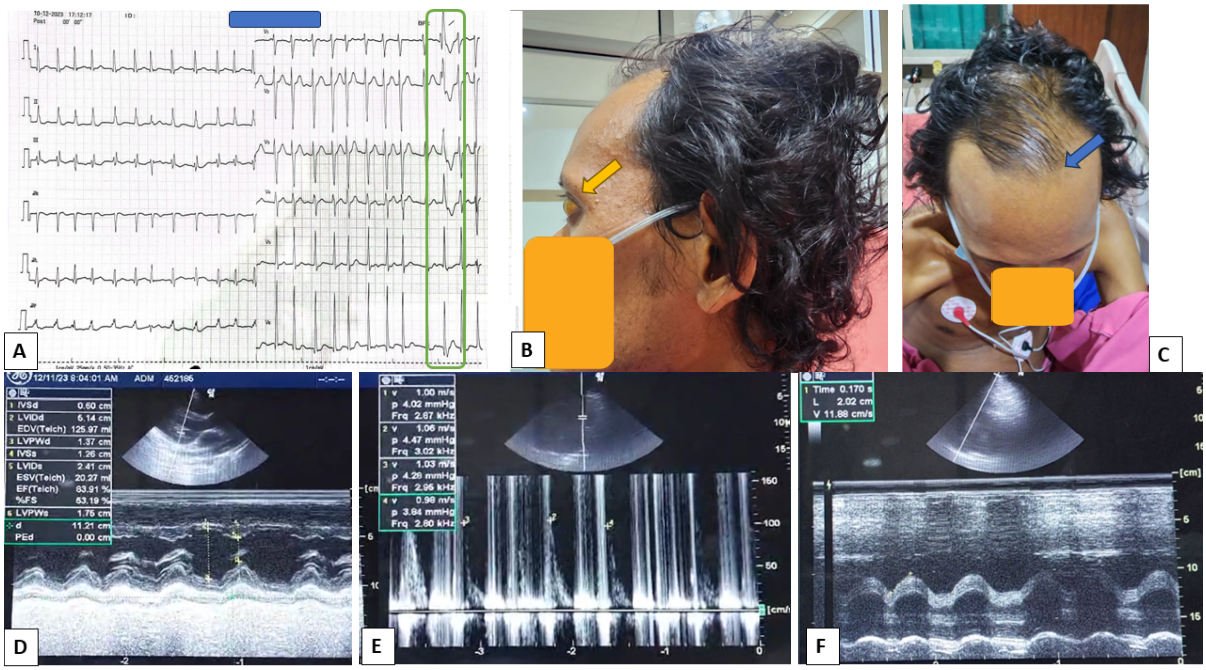

Figure 2. Clinical and hemodynamic echocardiogram profile of the patient.

Discussion

A thyroid storm is a rare and life-threatening exacerbation of hyperthyroidism, characterized by fever, delirium, seizures, coma, jaundice, arrhythmia, and high-output heart failure. The mortality rate due to cardiac failure, arrhythmia, or hyperthermia can be as high as 30%, even with appropriate treatment. TS is typically precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery—especially thyroid surgery—or radioiodine treatment in patients with partially treated or untreated hyperthyroidism. Patients with TS and hyperthyroidism exhibit different normal ranges of hemodynamic parameters due to the effects of thyroid hormones on the cardiovascular system; therefore, monitoring these parameters should be conducted with heightened vigilance.[3,5]

Thyroid hormones, particularly T3, exert positive inotropic and chronotropic effects, increasing heart rate and cardiac output. This ultimately results in decreased systemic vascular resistance as a hemodynamic response. However, in chronic states, this can lead to pathological shifts in hemodynamic and neurohumoral conditions. In the early stages, heart failure manifests as HFpEF, with diastolic dysfunction as the primary mechanism. In later stages, biventricular failure with Heart Failure with Reduced Ejection Fraction (HFrEF) may occur. Arrhythmias, primarily in the form of rapid atrial fibrillation, can lead to rate-related reductions in both left ventricular systolic and diastolic functions due to decreased ventricular filling. Right ventricular strain may also increase due to elevated pulmonary vascular resistance.[6]

From a metabolic perspective, hyperthyroidism also has a crucial role in the acceleration of atherosclerosis, thrombosis formation, and secondary hypertension, leading to hypertensive heart disease. Pre-existing ischemic or hypertensive heart disease may further impair the ability to compensate for hemodynamic and neurohumoral changes, particularly in TS.[3,6-7]

Hence, effective management requires intensive monitoring and supportive care, identifying and treating precipitating causes as well as adopting measures to reduce thyroid hormone synthesis. Fluid resuscitation with crystalloid solutions must be administered. Large doses of Propylthiouracil (500–1000 mg loading dose, maintenance 250 mg QID), or methimazole as an alternative at 20 mg QID, should be given. Stable iodide should be administered at 5 drops QID to block thyroid hormone synthesis. Glucocorticoids (hydrocortisone 300 mg IV bolus, then 100 mg TID, or methylprednisolone 50 mg IV) should be administered to reduce inflammation and inhibit the conversion of T4 to T3.[2,4,8] Propranolol of 20 mg to 80 mg every 6 to 4 hours can help control adrenergic symptoms, increase ventricular filling, and control the arrhythmia rate. However, caution is warranted due to the negative inotropic effects, especially in patients who are native beta-blocker users.[5–7]

We managed our case of TS and acute heart failure in a remote setting. The patient presented

with acute heart failure, atrial fibrillation with rapid ventricular response, and thyroid storm due to untreated Graves' disease. The patient exhibited signs of congestion and hyperdynamic function based on physical examination and echocardiography hemodynamic assessment (Table 1). There were no signs of hypoperfusion initially. Our first strategy was to alleviate congestion and manage heart failure with IV furosemide, ramipril, spironolactone, hydrochlorothiazide, and propranolol at an initial dose of 10 mg TID, which was titrated in the ICU to control tachycardia and TS. Digoxin IV 0.25 mg and warfarin 2 mg were administered for atrial fibrillation. The treatment for TS included methimazole and dexamethasone, given the unavailability of hydrocortisone and iodine. Unfortunately, we could not monitor our patients with invasive techniques. We could not recognize early signs of hypoperfusion due to the hemodynamic complexities in hyperthyroid patients. We identified that the patient was deteriorating and hypoperfusion state on the third day, following a decrease in urine output and the onset of delirium (Figure 1). We also initiated hemodynamic support on the fifth day, despite the patient having normal cardiac output and vascular resistance, due to persistent hypoperfusion and metabolic acidosis. There is ongoing debate regarding the aggressiveness of propranolol use in high-output states. Pulse-dose steroids are a potential rescue strategy; however, we did not implement this due to pneumonia infection, and we opted for high-dose dexamethasone.[9-10]

Table 1. Hemodynamic and lab profile.

Day 1: Admission	Day 3: Start deteriorating	Day 4	Day 6
Hemodynamic TD 169/103 (123) mmHg HR 135-148 bpm eRAP 15 mmHg SV 45-50 ml CO 6.5-7.4 L/min SVR 1167-1329 dyne/sec/cm^{-5} Peak E Vel 100 cm/s LVH Concentric Mild functional MR Mild-Trivial TR PvAcct 200 ms Diuresis 2.0 cc/kg/hr	TD 116/45 (63) mmHg HR 75-78 bpm eRAP 8 mmHg SV 52 ml CO 3.9-4 L/min SVR 1100-1128 dyne/sec/cm^{-5}	Norepinephrine 0.05 mcg/kg/min TD 100/45 (63) mmHg HR 70-78 bpm eRAP 8 mmHg SV 39 ml CO 3.0-3.2 L/min SVR 1375-1466 dyne/sec/cm^{-5}	Norepinephrine 0.05 mcg/kg/min Dobutamine 5 mcg/kg/min TD 92/45 (61) mmHg HR 80-85 eRAP 8 mmHg SV 40-45 ml CO 3.2-3.8 L/min SVR 1115-1325 dyne/sec/cm^{-5}
Lab Hb 15,4 g/dl Ht 47,6% Leucocyte 8430/mm^3 Tro 222.000/mm^3	Diuresis 0.8 cc/kg/hr	Diuresis 0.5 cc/kg/hr	Diuresis 0.3 cc/kg/hr
Renal Ur 45.1 mg/dl Cr 0.8 mg/dl eGFR (MDRD) 115	**Ureum 45 >> 95 mg/dl** **Cr 1.8 mg/dl** **eGFR 45.2**		
Other GDS 211 mg/dl Na 133 mEq/L K 4.1 mmol/L Cl 107 mEq/L SGOT 250 IU/L SGPT 300 IU/L	**Blood Gas Analysis** pH 7.26 pCO_2 45.2 pO_2 102 HCO_3 21.7 ABE -5.1 – metabolic acidosis (unable to measure lactate level)	**Abdominal Ultrasound** – Starry sky appearances – suggestive to acute (ischemic – hypoperfusion) Hepatitis	

Remote area settings present certain limitations. Blood Gas Analysis (BGA) had to wait several hours due to limited laboratory facilities; BGA examination was conducted at another hospital. We also faced challenges in obtaining invasive hemodynamic monitoring modalities. This modality is recommended by guidelines such as the Japanese Thyroid Storm Guidelines (2016). In this case, we relied heavily on echocardiographic hemodynamic examination. Additionally, we lacked advanced treatment modalities such as hemodialysis, plasmapheresis, mechanical support, or urgent total thyroidectomy in refractory critical settings.

Conclusion

Thyroid storm-induced acute heart failure may present a conundrum due to normotensive status and good cardiac output, potentially giving a false impression of the hemodynamic condition. Clinical presentation is crucial for identifying hypoperfusion, and aggressive treatment is necessary to stabilize the patient's condition.

List of Abbreviations

AF	Atrial Fibrillation
BGA	Blood Gas Analysis
CO	Cardiac Output
ECG	Electrocardiogram
eRAP	Estimated Right Atrium Pressure
fT4	Free Thyroxine Hormone (T4)
HFpEF	Heart Failure with Preserved Ejection Fraction
IV	Intravenous
LAVi	Left Atrial Volume Index
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
PAWP	Pulmonary Arterial Wedge Pressure
RV	Right Ventricle
SVR	Systemic Ventricular Resistance
TS	Thyroid Storm
TSH	Thyroid-Stimulating Hormone

Ethical Clearance

Not applicable. Written and informed consent was obtained from the parents of the patient.

Publication Approval

All authors consent to the publication of this manuscript.

Authors' Contributions

All authors contributed to the literature searching and review. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declared that they have no competing interests.

Availability of Data and Materials

All data supporting this case are contained within the manuscript. No additional datasets were generated or analyzed during the current study.

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