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Biomarker Profiles and Pathophysiological Pathways in Patients with Chronic Heart Failure and Metabolic Syndrome

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ABSTRACT

Heart failure is one of the leading causes of morbidity and mortality. Increased prevalence of metabolic syndrome is observed worldwide. Among heart failure, a significant number of patients also had metabolic syndrome. The pathophysiological link between those conditions is not yet established.

INTISARI

Gagal jantung menjadi salah satu penyebab utama kesakitan dan kematian. Peningkatan prevalensi sindrom metabolik telah merambah seluruh dunia. Di antara pasien dengan gagal jantung, sejumlah besar juga memiliki kondisi sindrom metabolik. Hubungan patofisiologis antara kedua kondisi tersebut belum diketahui.

INTRODUCTION

Metabolic syndrome represents cardiovascular risk factors, including insulin resistance, high blood pressure, lipid abnormalities, and obesity. These are associated with an increased risk of heart failure.[1] Based on NCEP-ATPIII criteria, metabolic syndrome is defined as individuals with three or more of the following characteristics: fasting blood sugar >100 mg/dL, blood pressure >130/85 mmHg, fasting triglyceride level >150 mg/dL, fasting HDL cholesterol level <40 mg/dL for males and <50 mg/dL for females and waist circumference > 40 inches in males and > 35 inches in females.[2]

The components of metabolic syndrome related as a risk factor for heart failure are hyperglycemia and insulin resistance, hypertension, lipid abnormality, and obesity.[3] Hyperglycemia and insulin resistance result in neurohormonal system activation, sympathetic nervous system activation, oxidative stress, free fatty acid myocardial utilization, abnormalities in contractile protein, endothelial dysfunction, and microvascular dysfunction.[3] Hypertension is associated with renin-angiotensin-aldosterone activation, apoptosis, and fibrosis. Lipid abnormality relates to increasing oxidative stress, inflammation, and lipotoxicity. Obesity has consequences of neurohormonal activation, sympathetic nervous system activation, adipokines imbalance, increased oxidative stress, cardiac steatosis, increased free fatty acid release, and lipotoxicity. All these mechanisms are related to the increased risk of developing heart failure in metabolic syndrome, which is a two-fold higher risk.[3]

The pathophysiological pathway linked to metabolic syndrome and heart failure is poorly documented. Whether those two conditions, comorbidities, or causalities are not yet confirmed. This review aims to report the role of biomarkers to elucidate the relationship between metabolic syndromes and heart failure.

Aritmia supraventrikular dapat terjadi pada PH yang lanjut. Fibrilasi atrium sendiri memiliki insiden pada 25% pasien setelah 5 tahun mengidap PH. Sedangkan aritmia ventrikel jarang terjadi.

Temuan rontgen pasien dengan PH diantaranya adalah dilatasi arteri pulmonal, disertai dengan pruning (kehilangan) pembuluh darah perifer. Jantung kanan yang melebar karena pembesaran ventrikel kanan terlihat sebagai penurunan ruang retrosternal pada gambar lateral. Meskipun demikian radiografi dada yang normal tidak menyingkirkan adanya PH.

BIOMARKERS IN METABOLIC SYNDROME WITH HEART FAILURE

The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) cohort is a multicentre, prospective, observational study of patients with worsening or new-onset heart failure. This study compromises two cohorts: an index cohort with 2516 patients from 11 European countries and a validation cohort with 1738 patients from Scotland.[4] The retrospective post-hoc analysis of BIOSTAT-CHF elucidates biomarkers analysis in metabolic syndrome and heart failure using multiplex immunoassay panels.[4] Multiplex

immunoassay panels consist of 363 protein biomarkers, with four panels: cardiovascular 2, cardiovascular 3, immune response, and oncology panels. The selected protein biomarkers are based on their established/putative role in distinct biologic in cardiovascular diseases, inflammation, immune response processes, or cancer.[4]

The result of this study showed that the established biomarkers associated with heart failure with metabolic syndrome are higher glucose level, higher bioadrenomedullin (bioADM) level, increased growth differentiation factor-15 (GDF-15) and lower NT-proBNP level.[4]

For novel biomarkers, the study indicated seven biomolecular pathways involved in the pathological process of heart failure and metabolic syndrome. These pathways are interleukin-10 signaling, natural killer cell-mediated cytotoxicity, mammary gland alveolus development, positive regulation of receptor-mediated endocytosis, endothelial cell apoptotic process, lipid export from cell, and regulation of neuroinflammatory response.[4] Among biomarkers linked with seven pathways, there are five most significantly elevated protein biomarkers, namely leptin, fatty acid binding protein (FABP)-4, interleukin (IL)-1ra, Tumor Necrosis Factor Receptor Superfamily Member (TNFRSF)11A, and RET.[4] The list of biomarkers associated with heart failure and metabolic syndrome are shown in Table 1.

Table 1. Biomarkers associated with heart failure and metabolic syndrome

Established biomarkers	Novel biomarkers
Increased glucose level	Increased leptin
Increased bioadrenomedullin	Increased FABP-4
Increased growth differentiatio factor-15	Increased TNFRSF11A
Reduced NT-proBNP	Increased RET

The expressed biomarkers in metabolic syndrome with heart failure are firmly related to obesity and chronic systemic inflammation. Adipose tissue functions as an endocrine organ. In obesity, adipose tissue secretes various pro-and anti-inflammatory by-products, which elevate in BioSTAT-CHF.[5] It links the pathophysiology of heart failure and metabolic syndrome.

Leptin is an energy-balancing hormone mainly secreted by adipocytes. Leptin suppresses the appetite to manage body weight and energy homeostasis. Individual with severe adiposity is associated with chronic hyperleptinemia and subsequent leptin resistance.[6] Leptin resistance leads to impaired appetite regulation and, therefore, the progression of obesity and other metabolic disorders. This pathological process increases the risk of heart failure.[6] Hyperleptinaemic state and insulin resistance found in obesity may induce IL-1ra and TNFRSF11A overexpression. IL-1ra has been shown to hinder leptin function and contribute to leptin resistance and promote a vicious cycle of obesity.[6] This condition explains that these systems increase in heart failure and metabolic syndrome.

FABP-4 secretion increased in obesity. FABP-4 is abundantly produced by epicardial adipose tissue and is a critical adipocytokine in patients with cardiovascular disease. FABP-4 induces insulin resistance and chronic low-grade inflammation in adiposity, associated with heart failure and metabolic syndrome.[7] RET, a proto-oncogene, is linked to higher GDF-15 in metabolic syndrome. GDF-15, a stress response cytokine, is already known as a prognostic marker for heart failure.[8] GDF-15 and RET have a shared receptor signaling pathway in metabolic regulation during stress; therefore, the elevation of RET is expected in patients with heart failure and metabolic syndrome.[8]

CONCLUSION

Metabolic syndrome is prevalent in patients with heart failure. Metabolic syndrome increases the risk of developing heart failure. In contrast, heart failure with metabolic syndrome is linked to a specific pathophysiological process, namely obesity and chronic inflammation state link metabolic syndrome and heart failure. Metabolic syndrome and heart failure are associated with increased concentration of biomarkers and activation of pathways related to lipid metabolism, obesity, and chronic inflammation.

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The Role of Angiotensin-receptor Blocker and Neprilysin Inhibitor (ARNI) in the Treatment of Heart Failure

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ABSTRACT

Heart failure is one of the leading causes of hospitalization, with nearly 44% of patients with all types of heart failure being admitted to the hospital for any reason within one year of discharge. The evidence-based pharmacological recommendation stated that the use of angiotensin-receptor blockers and neprilysin inhibitors (ARNI) for several phenotypes of heart failure is indicated to reduce hospitalization and death due to heart failure.

INTISARI

Gagal jantung menjadi penyebab utama perawatan di rumah sakit dengan hampir 44% pasien dirawat inap di rumah sakit dengan berbagai indikasi dalam satu tahun paska kepulangan. Rekomendasi penggunaan obat-obatan yang berbasis bukti menyebutkan bahwa penggunaan penyekat reseptor angiotensin dan penghambat nefrilisin (ARNI) pada beberapa fenotipe gagal jantung diindikasikan untuk mengurangi angka perawatan di rumah sakit dan kematian karena gagal jantung..

INTRODUCTION

Currently, the burden of heart failure reaches a worrisome condition. The number of patients is about 64 million adults worldwide living with heart failure. Furthermore, this number is expected to rise.[1] The vast majority of heart failure patients have three or more comorbidities.[1] Heart failure is a prime cause of hospitalization for patients aged >65 years.[2] For mortality, about 50% of heart failure patients die within five years from diagnosis.[2] The length of hospital stay following hospitalization for heart failure will increase as the disease complexity progresses.[2]

Heart failure is one of the leading causes of hospitalization for patients over 65 worldwide.[3] Nearly 44% of patients with all types of heart failure are admitted to the hospital for any reason within one year of discharge.[4] In those with hospitalized heart failure, the ensuing phase is chronic heart failure after stabilization and post-discharge period. Mortality during 30-day follow-up after heart failure hospitalization can reach 10%.[5] Around 25% of patients will be readmitted to the hospital within 30 days of follow-up.[5] Therefore, there is a need to optimize the medication for heart failure with evidence-based medicine-approved drugs. Angiotensin-receptor blocker and neprilysin inhibitor (ARNI) is a drug that is currently recommended as one pillar of heart failure pharmacological treatments. This review aims to update the current indication of ARNI in patients with heart failure.

ANGIOTENSIN-RECEPTOR BLOCKER AND NEPRILYSIN INHIBITOR (ARNI) AS ONE PILLAR OF HEART FAILURE TREATMENT

The primary mechanism of angiotensin-receptor blocker and neprilysin inhibitor (ARNI) hinders the renin-angiotensin-aldosterone system (RAAS) activation in heart failure. Currently, three drugs have been approved to treat heart failure in the RAAS system, namely angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA). The impact of ARNI is related to its ability to oppose the RAAS system by blocking angiotensin-1 receptors, done by valsartan as an ARB, and to impede neprilysin function. This endopeptidase cleaves various peptides, performed by sacubitril as a neprilysin inhibitor.

The blockade of angiotensin-1 receptors results in vasodilatation, which leads to reduced blood pressure, diminished sympathetic tone, decreased aldosterone level, and hindered fibrosis. The inhibition of neprilysin increases vasodilating peptides, producing vasodilating effects and finally reducing blood pressure.[6]

Table 1. Definition of heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) (from reference no. 7)

Type of hear failure	HFrEF	HFmrEF	HFpEF
Sign and symptoms	Positif	Positif	Positif
LVEF	≤ 40%	41% - 49%	≥ 50%
Other signs	No need	No need	Cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides

The current division of heart failure phenotype based on left ventricle ejection fraction (LVEF) is shown in Table 1.[7]. The ARNI is currently indicated for patients suffering from heart failure with reduced ejection fraction (HFrEF). In these patients, the addition of ARNI results in a 40% mortality reduction, exceeding the 20% reduction achieved by ACEI. The European Society of Cardiology (ESC) guideline for heart failure in 2021 stated that ACEI, beta-blockers, MRA, and dapagliflozin/empagliflozin are pharmacological treatments recommended for symptomatic HFrEF (LV EF ≤40%).[7] It is recommended that an ACEI or ARB is replaced by ARNI or sacubitril/valsartan in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with the above pharmacological agents. The alteration from ACEI or ARB to ARNI is beneficial for reducing the risk of heart failure, hospitalization, and death. In the 2022 AHA/ACC/HFSA guideline for managing heart failure, ARNI is recommended for patients with HFrEF NYHA functional class II-III.[8]

For patients with heart failure with mildly reduced ejection fraction (HFmrEF), ARNI is not indicated. However, the use of ARNI can be considered, along with other pharmacological pillars, for HFrEF. The weak recommendation for using ARNI in this population must be followed based on individual patient selection. Only diuretics as needed and SGLT2I are indicated in this patient population.[7,8]

In patients with heart failure with preserved ejection fraction (HFpEF), the ESC guideline does not recommend or consider using ARNI. The statements are similar to other heart failure pharmacological pillars.[7] However, in 2022, AHA/ACC/HFSA guidelines stated that ARNI can be considered in patients with HFpEF who are still symptomatic despite pharmacological treatment.[8]

Initiation of ARNI in patients hospitalized due to acute heart failure (AHF) is recommended both in ESC and AHA/ACC/HFSA guidelines. The ARNI is recommended as de novo treatment in hospitalized patients with AHF before discharge, given the improvement in health status, reduction in the prognostic biomarker NT-proBNP, and improvement of LV remodeling parameters compared with ACEI/ARB. The ARNI should be initiated de novo in patients hospitalized with AHF with reduced EF before discharge in the absence of contraindications.[8] Initiation of ARNI in recently hospitalized stable patients with HFrEF, including those who are ACEI/ARB naïve, is safe and may be considered in this setting.[7] In 2023 ESC statements, the intensive strategy of initiation and rapid up-titration of evident-based pharmacological treatment, including ARNI, before discharge and during frequent and careful follow-up in the first six weeks following AHF hospitalization is recommended. This strategy demonstrates the efficacy of reducing the risk of HF rehospitalization and death.[7]

CONCLUSION

The ARNI is currently becoming one pillar of heart failure management. The ARNI is recommended for first-line pharmacological therapy in patients with HFrEF. With careful selection, the ARNi can be considered as pharmacological management in patients with HFmrEF. For HFpEF, the ARNI is not recommended, but it may be considered in a particular population with symptoms. The ARNI can safely initiate in acute decompensated HF and de novo HF.

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Tailoring Antiplatelet Therapy for Patients with Antiplatelet Resistance

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Antiplatelet Resistance; Personalized Antiplatelet Therapy; Prasugrel; Clopidogrel, TRITON-TIMI 38 Study; PRASFIT-ACS Study; Major Adverse Cardiovascular Events (MACE); Escalation-De-escalation Strategy; Cardiovascular Outcomes; Treatment Tailoring; Risk Profiling; Acute Coronary Syndrome

ABSTRACT

Antiplatelet resistance, particularly concerning agents like clopidogrel, has become a significant issue in the management of cardiovascular diseases. In response to this concern, personalized antiplatelet therapy has emerged as an innovative approach to enhance therapeutic efficacy while ensuring patient safety. The TRITON-TIMI 38 study has positioned prasugrel as a superior alternative to clopidogrel, especially in patients with ACS undergoing PCI. Prasugrel's key attributes include its more potent antiplatelet effects, resulting in enhanced prevention of thrombotic events and a decreased incidence of MACE. These findings have not only reshaped the approach to antiplatelet therapy but have also presented prasugrel as a potential game-changer in cardiovascular care.

INTISARI

Resistensi antiplatelet, khususnya obat seperti clopidogrel, telah menjadi masalah penting dalam pengelolaan penyakit kardiovaskular. Menanggapi kekhawatiran ini, terapi antiplatelet yang dipersonalisasi telah muncul sebagai pendekatan inovatif untuk meningkatkan kemanjuran terapi sekaligus memastikan keselamatan pasien. Penelitian TRITON-TIMI 38 memposisikan prasugrel sebagai alternatif yang lebih unggul dibandingkan clopidogrel, terutama pada pasien SKA yang menjalani PCI. Keunggulan utama Prasugrel mencakup efek antiplateletnya yang lebih kuat, sehingga meningkatkan pencegahan kejadian trombotik dan penurunan kejadian MACE. Temuan ini telah mengubah pendekatan terapi antiplatelet dan menjadikan prasugrel sebagai terobosan potensial dalam perawatan kardiovaskular.

INTRODUCTION

Background

Cardiovascular diseases, such as myocardial infarction, stroke, and unstable angina, remain one of the leading causes of morbidity and mortality worldwide. These conditions have a profound impact on both individual patients and healthcare systems. Antiplatelet therapy, by mitigating the risk of thrombotic events, plays a pivotal role in the management of these diseases. Clopidogrel, a widely used thienopyridine antiplatelet agent, has been a standard treatment for patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI).

However, a significant concern that has arisen in clinical practice is the phenomenon of antiplatelet resistance. Antiplatelet resistance refers to the reduced response to antiplatelet agents, primarily clopidogrel, resulting in suboptimal therapeutic effects. Patients exhibiting antiplatelet resistance are at an increased risk of major adverse cardiovascular events (MACE) and poor clinical outcomes. The diverse genetic and clinical factors influencing antiplatelet resistance necessitate a tailored approach to antiplatelet therapy.

Prasugrel as a Superior Alternative

The TRITON-TIMI 38 study, a landmark clinical trial in the field of antiplatelet therapy, has made a significant contribution to the optimization of treatment strategies. This study showcased prasugrel, another thienopyridine antiplatelet agent, as a superior alternative to clopidogrel, especially in patients with ACS undergoing PCI. Prasugrel's key attributes include its more potent antiplatelet effects, resulting in enhanced prevention of thrombotic events and a decreased incidence of MACE. These findings have not only reshaped the approach to antiplatelet therapy but have also presented prasugrel as a potential game-changer in cardiovascular care.

Role of Clopidogrel

While prasugrel's emergence as a potent antiplatelet agent is commendable, it is essential to acknowledge that clopidogrel continues to hold a significant place in the spectrum of antiplatelet therapy. Its well-established track record, cost-effectiveness, and wide availability make it an essential component in the treatment of cardiovascular diseases. Hence, the coexistence of clopidogrel and prasugrel underscores the need for a personalized and nuanced approach to antiplatelet therapy, maximizing the benefits of both agents.

Personalized Antiplatelet Therapy

The "Escalation-De-escalation" Strategy

Personalized antiplatelet therapy introduces a strategic approach known as the "Escalation-De-escalation" strategy. This innovative approach aims to optimize therapeutic choices for individual patients by tailoring the selection of antiplatelet agents based on their unique responses.

Prasugrel vs. Clopidogrel Selection

Patients who display resistance to clopidogrel or are identified as high-risk candidates due to genetic or clinical factors become eligible for the potent antiplatelet effects of prasugrel. Prasugrel's superior inhibition of platelet activation and aggregation makes it an effective choice in such cases. On the other hand, clopidogrel, with its established safety profile, may continue to serve as a suitable option for patients who are responsive to the drug.

Rationale for "Escalation" and "De-escalation"

The rationale for the "Escalation-De-escalation" strategy is rooted in the significant variability in patients' responses to standard antiplatelet agents. Antiplatelet resistance is not solely influenced by genetic factors but also by clinical parameters and comorbid conditions. As a result, the traditional one-size-fits-all approach to antiplatelet therapy is suboptimal, often leading to less favourable clinical outcomes.

The "Escalation" phase involves initiating treatment with prasugrel for high-risk patients, ensuring the most effective antiplatelet inhibition. This approach is based on the principle that patients with a higher thrombotic risk necessitate more potent antiplatelet agents.

In the "De-escalation" phase, patients not exhibiting resistance or at high risk for MACE can safely continue with clopidogrel. This approach minimizes the risk of bleeding complications associated with more potent agents, aligning therapy with individual patient profiles.

The PRASFIT-ACS Study

The PRASFIT-ACS study, which focuses on patients with Acute Coronary Syndrome, further underscores the merits of prasugrel in the context of personalized antiplatelet therapy. ACS is a critical cardiovascular condition, characterized by myocardial infarction and unstable angina, in which antiplatelet therapy plays a crucial role in preventing adverse events. This study's outcomes underscore the potential benefits of personalized antiplatelet therapy, emphasizing that it can significantly enhance patient care in cases of ACS.

Benefits and Challenges of Personalized Antiplatelet Therapy

Benefits

Personalized antiplatelet therapy offers several notable advantages:

- Enhanced Efficacy: By tailoring the choice of antiplatelet agents to individual patient profiles, the therapy significantly enhances its effectiveness in preventing thrombotic events.
- Improved Patient Safety: Personalized therapy minimizes the risk of antiplatelet resistance, reducing the likelihood of MACE.
- Cost-effectiveness: By choosing the most appropriate antiplatelet agent for each patient, the therapy optimizes resource utilization and minimizes unnecessary expenses.
- Increased Patient Adherence and Satisfaction: A personalized approach aligns therapy with patients' unique profiles, increasing adherence to treatment and patient satisfaction.

Challenges

Despite its promising merits, personalized antiplatelet therapy is not without its challenges. These include:

- Comprehensive Risk Profiling: The need to develop and implement comprehensive risk profiling methods to identify patients who would benefit most from prasugrel.
- Optimizing Medication Dosages: Ensuring that patients receive the right dosage of the selected antiplatelet agent is essential, as both overmedication and undermedication can have adverse effects.
- Resource Allocation: Addressing issues related to cost and resource allocation to ensure that personalized antiplatelet therapy is accessible to all patients.

Conclusion

The combined insights from the TRITON-TIMI 38 and PRASFIT-ACS studies underscore the merits of personalized antiplatelet therapy in cardiovascular care. This tailored approach offers a viable solution to the issue of antiplatelet resistance, optimizing therapeutic choices based on individual patient profiles. By employing the "Escalation-De-escalation" strategy, healthcare professionals can revolutionize cardiovascular care, ultimately leading to improved clinical outcomes and enhanced patient safety. Personalized antiplatelet therapy is poised to transform the landscape of cardiovascular care, offering a tailored solution that acknowledges the unique needs of each patient. It represents a significant

advancement in the pursuit of personalized medicine in the field of cardiology.

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Renal Support in ICCU: Focusing on Continuous Renal Replacement Therapy Management

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ABSTRACT

Acute kidney injury (AKI) are common in the Intensive Cardiovascular Care Unit (ICCU). AKI may be accompanied by metabolic, acid-base, electrolyte disturbances and fluid overload. AKI may affect other organ systems and may require immediate treatment. Management of AKI plays an important role in morbidity & mortality. Renal support is important in management patient with cardiac problem. One of the treatment options for AKI is using renal replacement therapy (RRT). There are intermittent and continuous RRT (CRRT).

CRRT provides slow, continuous and gentle replacement of renal function. CRRT closely mimics the native kidney in treating AKI and fluid overload. Its removes large amounts of fluid and waste products (urea, creatinine) over time, re-establishes electrolyte and pH balance and tolerated well by hemodynamically unstable patients. *Systemic inflammatory response syndrome* (SIRS) often occurs in patients with cardiogenic shock. CRRT has the advantage of overcoming SIRS conditions. There are several modes of CRRT therapy, i.e. SCUF (Slow Continuous Ultrafiltration), CVVH (Continuous Veno-Venous Hemofiltration), CVVHD (Continuous Veno-Venous HemoDialysis) and CVVHDF (Continuous Veno-Venous HemoDiaFiltration). Each of these modes can be used according to the needs and clinical conditions of the patient.

INTISARI

Cedera ginjal akut (AKI) sering terjadi di Unit Perawatan Kardiovaskular Intensif (ICCU). AKI dapat disertai dengan gangguan metabolisme, asam basa, elektrolit, dan kelebihan cairan. AKI dapat mempengaruhi sistem organ lain dan memerlukan manajemen segera. Penatalaksanaan AKI memegang peran penting terhadaap kejadian morbiditas dan mortalitas. Terapi pendukung ginjal penting dalam tatalaksana pasien dengan masalah jantung. Salah satu pilihan terapi AKI adalah dengan menggunakan terapi pengganti ginjal (RRT). RRT ada yang bersifat intermiten dan kontinyu (CRRT).

CRRT bekerja secara perlahan dan terus menerus dalam membantu fungsi ginjal yang mengalami AKI. Prinsip kerja CRRT sangat mirip dengan ginjal alamiah dalam upaya mengatasi AKI dan kelebihan cairan. CRRT dapat digunakan untuk mengeluarkan sejumlah besar cairan dan produk limbah (urea, kreatinin), sehingga bermanfaat dalam mengembalikan keseimbangan elektrolit dan pH serta dapat ditoleransi dengan baik oleh pasien yang hemodinamiknya tidak stabil. *Systemic Inflammatory Response Syndrome* (SIRS) sering ditemukan pada pasien yang mengalami syok kardiogenik. CRRT memiliki keunggulan dalam mengatasi kondisi SIRS. Ada beberapa mode terapi CRRT, yaitu SCUF (Slow Continuous Ultrafiltrasi), CVVH (Continuous Veno-Venous Hemofiltrasi), CVVHD (Continuous Veno-Venous HemoDialysis) dan CVVHDF (Continuous Veno-Venous HemoDiaFiltration). Masing-masing mode tersebut dapat digunakan sesuai dengan kebutuhan dan kondisi klinis pasien.

INTRODUCTION

Acute kidney injury (AKI) is results from the sudden loss of kidney function. AKI is defined by an abrupt decrease in kidney function that includes, but is not limited to, acute renal failure (ARF). It is a broad clinical syndrome encompassing various etiologies.[1]

There are 3 types of AKI, i.e. pre-renal, intrinsic and post-renal. Pre-renal causes of AKI is usually results from decreased blood flow to the kidneys. Examples of situations leading to pre-renal failure may include dehydration, haemorrhage, congestive heart failure and shock. Intrinsic renal causes of AKI typically involves direct injury to the kidney itself. The most common cause is acute tubular necrosis (ATN). In post-renal AKI, the underlying cause occurs in both kidneys or in a single functioning kidney. Causes for this may be related to tumour development or urinary tract obstruction.[2] In short, the main cause of AKI could be include ischemia, hypoxia or nephrotoxicity.[3]

AKI is defined as any of the following: increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours. AKI also staged for severity according to the Table 1.[1]

AKI may be accompanied by metabolic, acid-base & electrolyte disturbances and fluid overload. AKI may affect other organ systems and may require immediate treatment.[4] Management of AKI plays an important role in morbidity & mortality. One of the treatment options for AKI is using renal replacement therapy (RRT). There are intermittent and continuous RRT (CRRT).

DISCUSSION

Acute kidney injury (AKI) are common in the Intensive Cardiovascular Care Unit (ICCU). Prevalence of AKI was evaluated at 22% in hospital settings in a large meta-analysis and raised up to 57% when admitted to intensive care units.[5,6] The incidence of dialysis-requiring AKI has increased in the United States.[7] AKI has a significant association with high mortality in critically ill patients.[8,9] RRT is frequently required to manage critically ill patients with AKI. It is widely used as a supportive management of severe AKI and multiorgan failure (MOF).

RRT used in daily practise can be separated into three modalities; intermittent hemodialysis (IHD), prolonged intermittent RRT (PIRRT) (also called sustained low-efficiency dialysis [SLED]), and continuous RRT (CRRT).

Continuous renal replacement therapy (CRRT), in particular, is utilised for a haemodynamically unstable patient with AKI in an intensive care unit (ICU) setting. CRRT allows for continuous, slow and isotonic fluid removal that results in better haemodynamic tolerance even in unstable patients with shock and severe fluid overload. CRRT can be modified at any time to meet the rapidly changing haemodynamic situation of critically ill patients. CRRT includes several treatment modalities i.e. ultrafiltration, convective therapy, diffusive therapy or diffusive & convective therapy. The choice of therapy will depend on the needs of the patient, the preferences of the physician.[10]

The use of CRRT aims to clean the blood (remove waste), which is achieved through diffusion and convection. Another function of CRRT is to manage intravascular volume, through ultrafiltration mechanisms.[10] Indications for CRRT use include renal and non-renal indications. Renal indications are to reduce serum urea and creatinine, treat hyperkalemia conditions that do not respond to medical treatment, improve severe metabolic acidosis conditions, and treat oliguria/anuria conditions that are resistant to diuretic use. Meanwhile, non-renal indications include include correcting electrolyte abnormalities, clearing ingested toxins, managing fluid balance in heart failure, and removing inflammatory mediators in sepsis.[11]

Principles guiding blood-based extracorporeal in CRRT include diffusion, ultrafiltration and convection. Diffusion, as used in hemodialysis, is the movement of solutes across a semipermeable membrane. The direction and intensity of that movement are driven by the concentration gradient (from higher to lower). Ultrafiltration is the movement of fluid across a semipermeable membrane using pressure differential (from higher to lower pressure) to generate the ultrafiltrate. Meanwhile, convection, as used in hemofiltration, is the clearance of dissolved solutes along plasma crossing the semipermeable membrane (ultrafiltrate) (a mechanism sometimes called “solvent drag”).[12]

CONCLUSION

Renal support is important in the management of patients with underlying cardiac problems. CRRT is considered the first line when managing critically ill patients with haemodynamic instability. Patients in the ICCU have complex problems, not only heart problems, but can be accompanied by other comorbidities such as sepsis. CRRT has the advantage that apart from being able to be used for renal indications, it is also useful for non-renal indications, one of which is if the patient experiences sepsis.

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When to Put Implantable Cardioverter Defibrillator in Channelopathy and Infiltrative Cardiomyopathy

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ABSTRACT

Background: It is known that many previously unexplained sudden cardiac deaths (SCDs) and life-threatening ventricular arrhythmias in young people are genetic in origin and are linked to an increasing number of unique inherited arrhythmogenic diseases. Most genetic arrhythmias are associated with either infiltrative cardiomyopathy or cardiac ion channel diseases, also known as channelopathies. The best treatment for preventing SCD is an implantable cardioverter defibrillator (ICD).

Discussion: The indications for ICD in channelopathies are patients who experience arrhythmogenic syncope (particularly in patients on highest tolerated therapeutic medications dose), have documented spontaneous sustained ventricular tachycardia (VT), or are survivors of an aborted cardiac arrest. To prevent SCD in infiltrative disease, ICD is indicated mainly in patients with haemodynamically intolerable VT or aborted cardiac arrest.

Conclusion: It is crucial to implant ICD in these patients to prevent arrhythmic death.

INTISARI

Latar Belakang: Kematian Jantung Mendadak (KJM) yang tidak dapat dijelaskan dan Aritmia Ventrikuler pada populasi muda umumnya disebabkan karena genetik dan dikaitkan dengan peningkatan jumlah penyakit aritmogenik bawaan. Kebanyakan aritmia genetik berhubungan dengan kardiomiopati infiltrative dan gangguan kanal ion jantung, yang juga dikenal dengan kanalopati. Tatalaksana terbaik untuk mencegah KJM adalah dengan pemasangan *Implantable Cardioverter-Defibrillator* (ICD).

Diskusi: Indikasi pemasangan ICD pada kanalopati adalah pasien dengan sinkop aritmogenik (terutama pada pasien yang tidak respon dengan pemberian medikamentosa dosis tinggi), memiliki riwayat takikardia ventrikuler, atau memiliki riwayat henti jantung. Untuk mencegah KMJ pada penyakit infiltratif, pemasangan ICD diindikasikan terutama pada pasien takikardia ventrikuler dengan hemodinamik yang tidak stabil.

Kesimpulan: Penting untuk melakukan implantasi ICD dalam pencegahan kematian aritmik pada pasien-pasien ini.

INTRODUCTION

Sudden cardiac death (SCD) is a major worldwide health burden. Even though SCD mainly occur in coronary artery disease and heart failure patients, it can also occur in healthy patients without overt heart disease.[1] Many previously unexplained sudden cardiac deaths (SCDs) and life-threatening ventricular arrhythmias (VAs) in young people are genetic in origin and are linked to an increasing number of unique inherited arrhythmogenic diseases, including channelopathies and infiltrative cardiomyopathies.[1–3]

Despite being less common in the population under the age of 35 due to the numerous potential etiologies and frequently unsolved concerns, the incidence of SCD in the young population raises concern. It is crucial to implement available screening methods and early diagnosis approach in this population due to its tragic nature.[3]

Due to a lack of data from randomized clinical trials, it is difficult to define appropriate selection criteria for implanting an implantable cardioverter-defibrillator (ICD) in these patients. As a result, current guidelines rely more on non-randomized studies and expert opinions to make their recommendations.[4] This article aims to discuss when to implant ICD in channelopathies and infiltrative cardiomyopathies.

DISCUSSION

ICD History, Indications, Models, and Mechanisms

ICD was invented by a Polish physician, Mieczyslaw (Michel) Mirowski. His friend's death due to Ventricular Tachycardia (VT) inspired his idea of implanting an automatic defibrillator. The first device implanted in a human was called an automatic implantable defibrillator (AID). The name of the device was eventually changed to AICD (Automatic Implantable Cardioverter-Defibrillator), which was then abbreviated in common usage to ICD, as it was considered that the acronym conveyed that ventricular fibrillation (VF) was the only arrhythmia that the device treated.[5]

ICD implantation is the mainstay of primary and secondary SCD prevention worldwide. Primary prevention is an effective approach for patients who are more at risk for such an event than secondary prevention, which is defined by individuals who have undergone a symptomatic life-threatening persistent VT or VF.[2]

ICD consists of three components; the generator, the leads, and the shocking coil. The advanced technology that reads, interprets, and saves cardiac rhythm tracings as well as determines when and how to administer the proper therapy (ATP or defibrillation) is housed in the ovoid or circular pod known as the pulse generator or generator. It is often placed in the subcutaneous pocket in the pectoral region.[6]

The silicone-coated wires or cables known as leads, which stay inside the heart, connect the generator to the myocardium and include the electrodes that allow for easy conduction between the device and the myocardial. At one end, they are attached to the device by screws, and at the cardiac end, the lead is fixed inside the appropriate heart chamber by screws or tines.[6]

An ICD also has a coil that supplies the appropriate charge for defibrillation/electrical cardioversion is built into the lead of the ICD. The presence of shocking coils, which appear as localized and clearly defined spiral thickenings on the lead and are often located around the SVC on atrial leads and close to the ventricular end of RV leads, can be used to identify ICD leads on plain radiograms.

ICD Implantation in Indonesia

Even though the ICD implantation rate in Indonesia tripled in the past decade, the ratio still lags behind other Southeast Asian countries with smaller populations (Figure 1).[7,8] There are various obstacles to tackle to increase the rate of ICD implantation in Indonesia, mainly the limited financial resources, lack of centers, trained personnel and the low awareness of guidelines.[8]

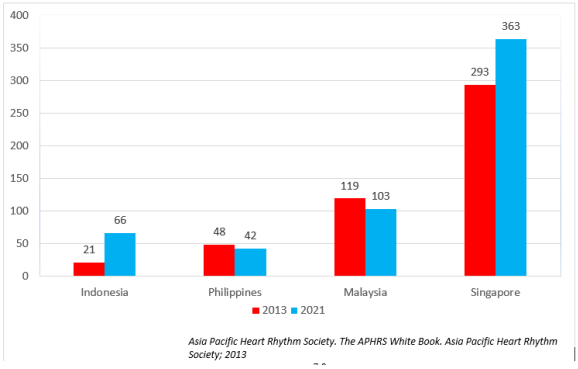


Figure 1. ICD implantation in Southeast Asian Countries. Indonesia's ICD implantation rate have tripled in the previous ten years but still lags behind other Southeast Asian nations with smaller populations.[7,8]

Channelopathies

Cardiac channelopathies occur when there are changes in the genes that are linked to different channels in the heart's membranes (Long QT Syndrome, Short QT Syndrome, and Brugada Syndrome) or cellular structures affecting Ca2+ availability (several forms of CPVT). The first line therapy usually involves medications. However, ICD implantation has a clear role for secondary prevention of SCD in patients who have already had a major heart event. On the other hand, ICD implantation for primary prevention is still controversial.[9]

Brugada Syndrome

Southeast Asia has the highest Brugada Syndrome (BrS) burden. However, the majority of current research is from Western countries. The estimated prevalence of asymptomatic BrS (ECG Type 1) and Type 2/3 BrS in Asia ranges from 0.00% to 1.77% and 0.014% to 15.96%, respectively, according to the suggested Shanghai grading system (Figure 2).[10]

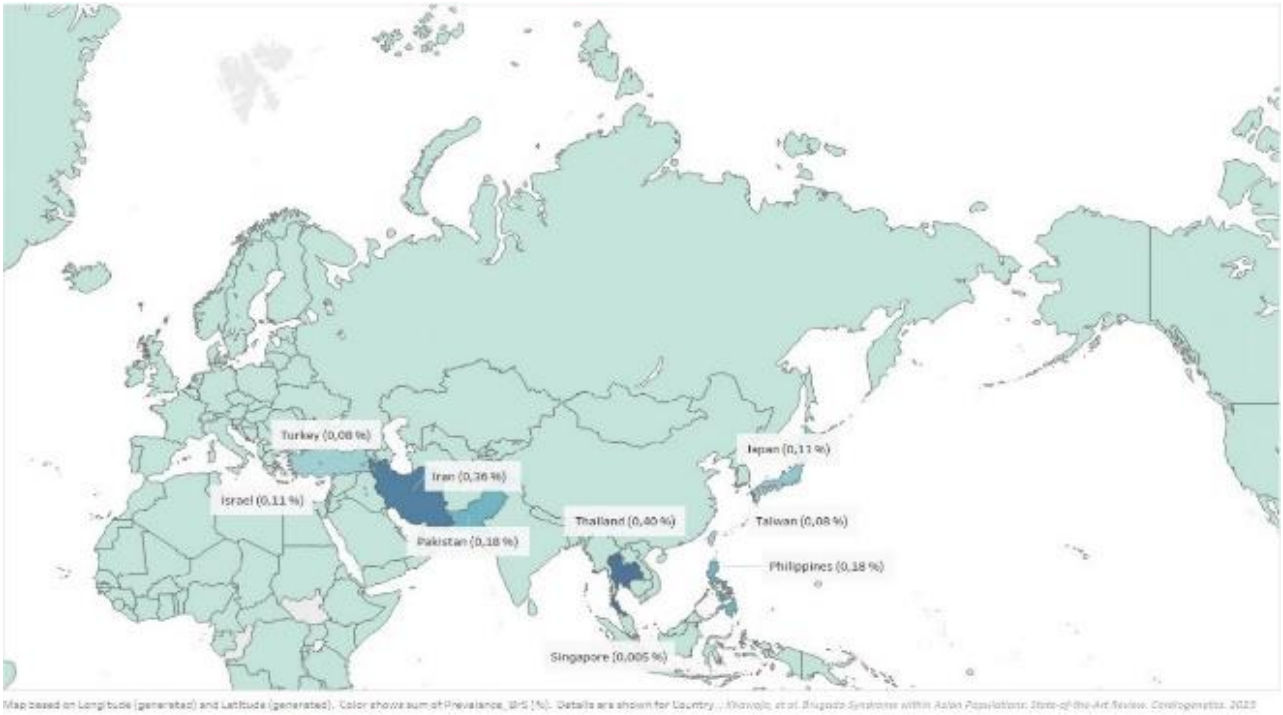


Figure 2. Brugada Syndrome in Asia. The estimated prevalence of asymptomatic BrS in Asia ranges up to 1.77% (type 1) and up to 15.96% (type 2/3) according to the suggested Shanghai grading system.[10]

ICD implantation for BrS patients is recommended for those who are survivors of an aborted CA and/or have documented spontaneous sustained VT (Class I recommendation, Level of Evidence C). Patients with ECG suspicious of Brugada Syndrome must be excluded from alternative diagnosis consistent with their ECGs. Beside patients with spontaneous type 1 BrS ECG, patients with positive sodium channel blocker test is also recommended for ICD implantation (Class I recommendation). Figure 3 shows the algorithm of BrS patients management. [11]

Long QT Syndrome

Long QT Syndrome (LQTS) occurs in about 1 out of every 20,000 to 1 out of every 5,000 people. Based on the nongenotyped infants with QTc between 451 and 470 ms, it is estimated that the prevalence of LQTS is around 1 in 2000.[12] The LQTS prevalence may actually be higher than what has been reported, because up to 37% of people with genotype-confirmed LQTS may have a normal QTc interval (i.e. concealed LQTS).[13]

The QT interval is not the sole diagnostic parameter for LQTS. **Table 1** shows the Modified LQTS diagnostic score, which includes the patient's clinical history, family history, and genetic finding.[11]

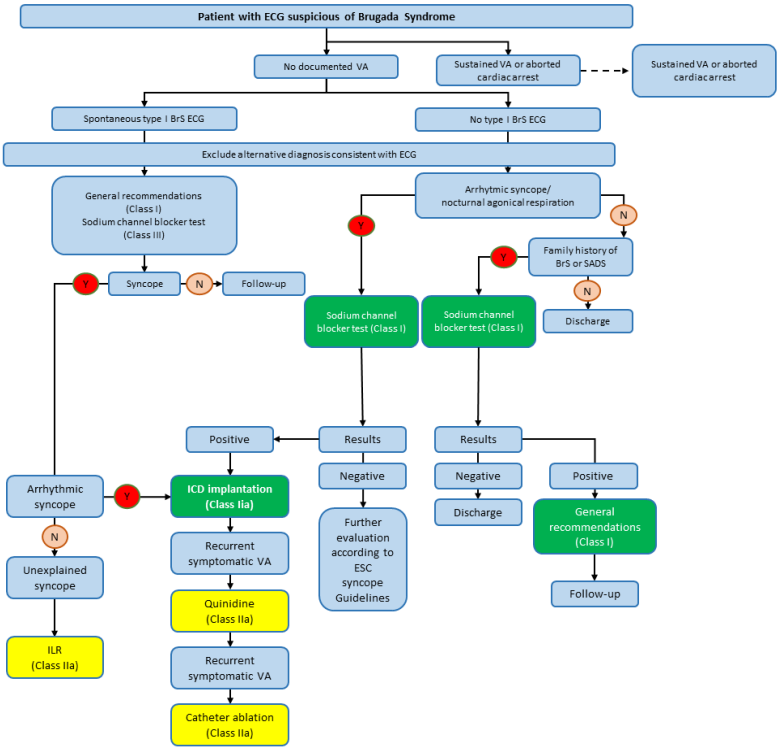
Beside beta-blockers, ICD implantation is recommended in LQTS patients with cardiac arrest (Class I, LoE B), in symptomatic LQTS patients despite receiving beta-blockers and genotype-specific therapies (Class I, LoE C). ICD implantation should also be considered in patients with symptomatic LQTS with intolerance or contraindication to beta-blockers and genotype-specific therapies (Class IIa, LoE C). Figure 4 shows the algorithm of LQTS patients management.[11]

Table 1. Modified LQTS Diagnostic score[11]

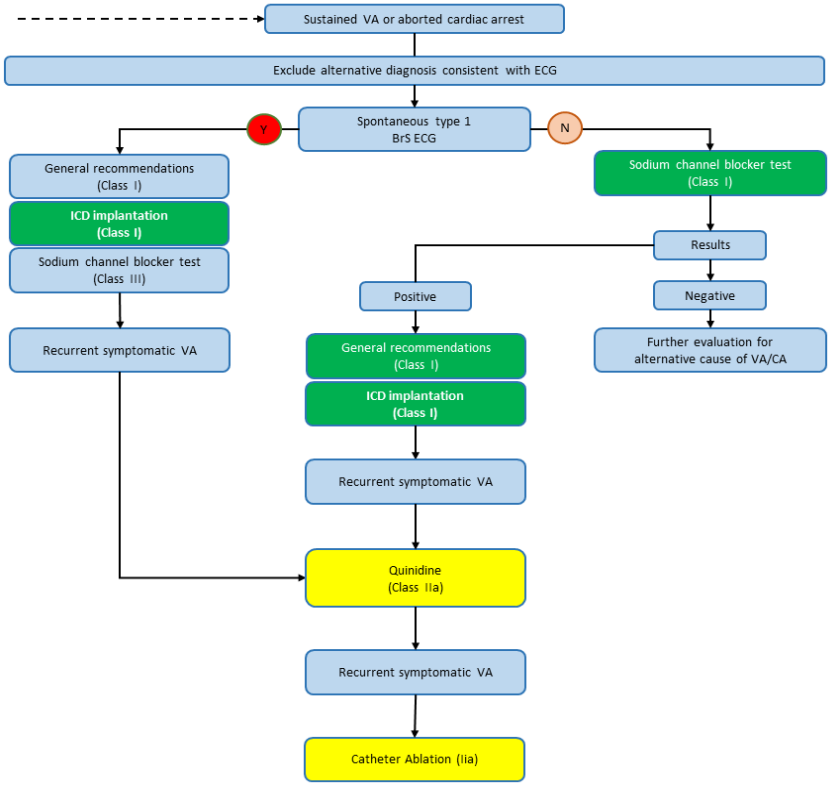
Findings			Points
ECG	Q′c	≥480 ms	3.5
		=460–479 ms	2
		=450–459 ms (in males)	1
		≥480 ms during 4th minute of recovery from exercise stress test	1
	Torsade de pointes		2
	T wave alternans		1
	Notched T wave in 3 leads		1
	Low heart rate for age		0.5
Clinical history	Syncope	With stress	2
		Without stress	1
Family history	Family member(s) with definite LQTS		1
	Unexplained SCD at age 30 years in first degree family		0.5
Genetic finding	Pathogenic mutation		3.5

Short QT Syndrome

Diagnosis of Short QT Syndrome (SQTS) can be made of a QTc ≤ 320 ms alone, or a QTc ≤ 360 ms combined with a family history of SQTS, aborted CA in the absence of heart disease or pathogenic mutation.[14] In SQTS patients, ICD implantation is recommended for those who survived an aborted CA and/or have documented spontaneous sustained VT (Class I, LoE C) and should be considered in patients with arrhythmic syncope (Class IIa, LoE C).[11]



(A)



(B)

Figure 3. Management algorithm in Brugada Syndrome patients without a history of aborted CA (A) and with a history of aborted CA (B). ICD implantation is recommended in BrS with a history of aborted CA and patients with positive sodium channel blocker test.[11]

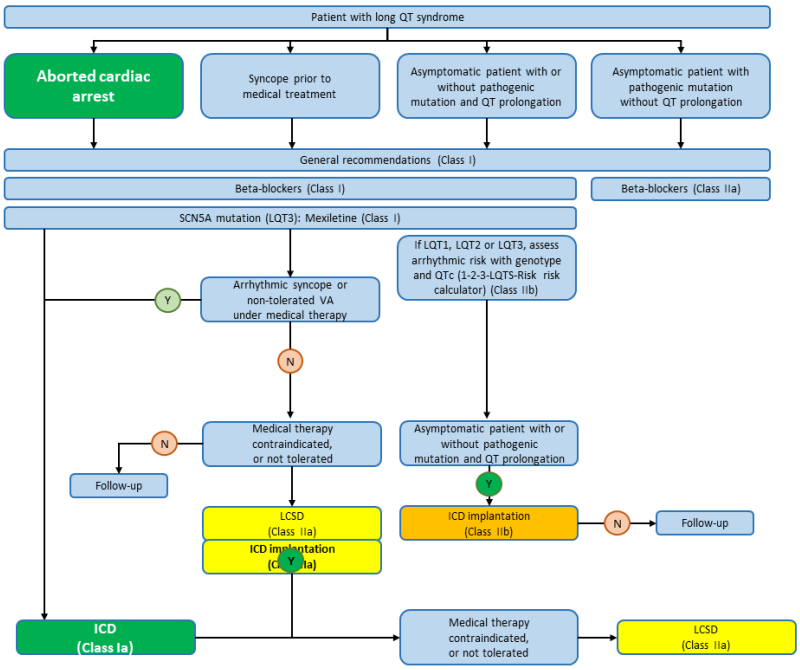


Figure 4. Management algorithm in LQTS patients**.** ICD implantation is recommended in LQTS patients with cardiac arrest, those who are symptomatic despite optimal medical therapy. ICD implantation should be considered symptomatic LQTS patients with medical therapies.[11]
LCSD: Left Ventricular Sympathetic Denervation

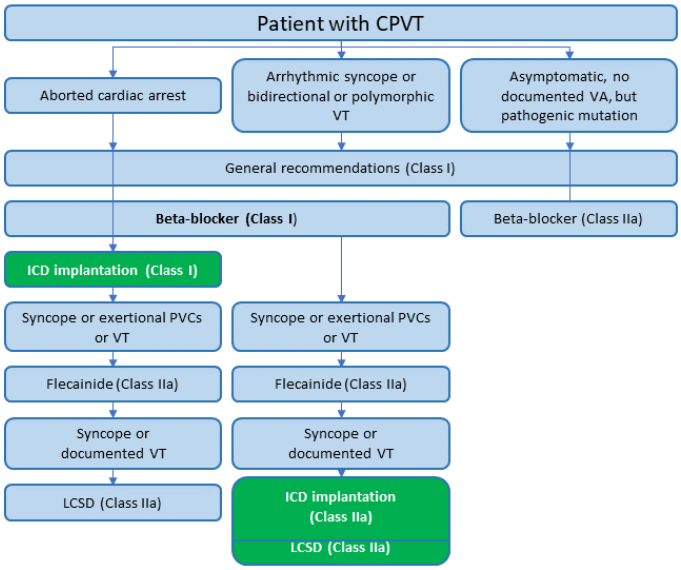


Figure 5. Management algorithm in CPVT patients. ICD is recommended in CPVT patients following an aborted CA, who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on medical therapy.[11]

Catecholaminergic Polymorphic Ventricular Tachycardia

ICD implantation combined with beta-blockers and flecainide is recommended in Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) patients following an aborted CA (Class I, LoE C). Meanwhile, CPVT patients who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on highest tolerated beta-blocker dose and on flecainide are recommended for ICD implantation (Class IIa, LoE C). Figure 5 shows the algorithm of CPVT patients management.[11]

Infiltrative Cardiomyopathy

Other diseases that may need ICD are infiltrative cardiomyopathies. Infiltrative cardiomyopathy is defined as cardiac disease in which the ventricular walls become rigid due to abnormal substance deposition, thereby impending ventricular filling. Due to the relative rarity of these disorders, accurate diagnosis requires a high level of clinical suspicion. Depending on the cause and severity of the illness, treatment may include medication, device therapy, and, in some situations, organ transplantation.[15] Common types of infiltrative cardiomyopathies are listed in **Table 2**.[16]

Table 2. Common types of infiltrative cardiomyopathies[16]

CONDITION	EPIDEMIOLOGY	PATHO-LOGY	ECG	ECHO-CARDIOGRAM	CMR	TREATMENT
Cardiac amyloidosis	6th or 7th decade acquired (AL, SSA) or inherited (ATTR)	Extracellular amyloid fibrils	Low-voltage QRS; pseudo-infarction; AV block	LV and RV hypertrophy; granular speckled myocardium; restricted basal longitudinal strain	Global LGE (Also consider radionuclide scanning)	AL: chemotherapy (CyBordD); TTR: difflunisal/tafamidis; ± heart-liver transplant
Cardiac Sarcoidosis	3rd or 4th decade; African Americans, northern Europeans, Japanese; female>male	Noncaseating granulomas surrounded by fibrosis	High-grade AV block	Septal thinning/ thickening; noncoronary segmental wall motion abnormalities	Pathy LGE, predominantly LV free wall and basal septum (Also consider FDG-PET)	Corticosteroids, PPM/IC D; ± cardiac transplant
Hemochromatosis/ IOC	4th or 5th decade; inherited (primary, HFE mutation) or acquired (secondary)	Intracellular iron	Non-specific repolarization abnormalities	Diastolic disease global systolic dysfunction	Shortened T2* time	Phlebotomy; chelation

According to more recent observational studies, ICDs may be helpful in these patients' main prevention of SCD. Pacemakers and ICDs should be used with caution because of the high prevalence of SCD in these patients, as these interventions are potentially acutely lifesaving.[16] However, not all infiltrative cardiomyopathy patients need ICD implantation.

Amyloidosis

One of cardiomyopathy type that may require ICD implantation is cardiac amyloidosis.[16] Immunoglobulin light chain (AL) amyloidosis, the most common doem of systemic amyloidosis, is caused by a plasma cell clone infiltrating the bone marrow. This may lead to multi-organ damage, including the heart, which is the most important prognostic factor. Its mortality rate is up to 37% within 6 months of diagnosis.[17] **Figure 6** shows amyloidosis survival by year since the first diagnosis. The global epidemiology of this illness has only been briefly studied, shown in **Figure 7.** The epidemiological estimations for AL amyloidosis show the condition's rarity around the world and help to comprehend the full severity of the illness, which is essential for raising awareness and advancing research and the development of novel treatment options.[18] ICD should be considered in AL patients with hemodynamically not-tolerated VT (Class IIa, LoE C).[11]

Sarcoidosis

Cardiac sarcoidosis is a rare disease with a poor prognosis which is caused by granulomatous inflammation of the heart. Heart failure and abnormalities of the conduction system are its most prevalent clinical manifestations. Palpitations, pre-syncope, and syncope are the most typical presenting signs with cardiac sarcoidosis. These palpitations may be caused by numerous conduction disorders, such as AV blocks, atrial fibrillation, or other supraventricular tachycardias. Syncope and presyncope may be signs of high-grade AV block or VT, both of which can cause sudden cardiac death.[19] Cardiac sarcoidosis is one of the reasons for ICD implantation in Japan (**Figure 8**).[20]

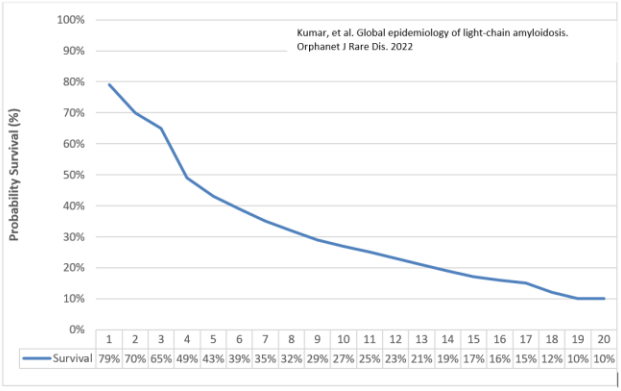


Figure 6[18]

Cardiac sarcoidosis patients with aborted CA or sustained VT or LVEF ≤35% is recommended for ICD implantation (Class I). Cardiac sarcoidosis patients who are also indicated for permanent pacing or with significant LGE should be considered for ICD implantation (Class IIa). Management of cardiac sarcoidosis patient is shown in **Figure 9.**[11]

CONCLUSION

SCD is a significant public health burden. Channelopathies and cardiac infiltrative diseases are not easy to diagnose to begin with, since patients may first present with severe arrhythmias or even cardiac arrest. Diagnostic tools

become the outmost importance. ICD is an effective therapy for SCD prevention in channelopathies and infiltrative diseases. However, ICD implantation is even more challenging, particularly in Indonesia. This is because ICD accessibility, public awareness, and education on SCD prevention is still low. We should focus on near term prevention and improvement in SCA outcome.

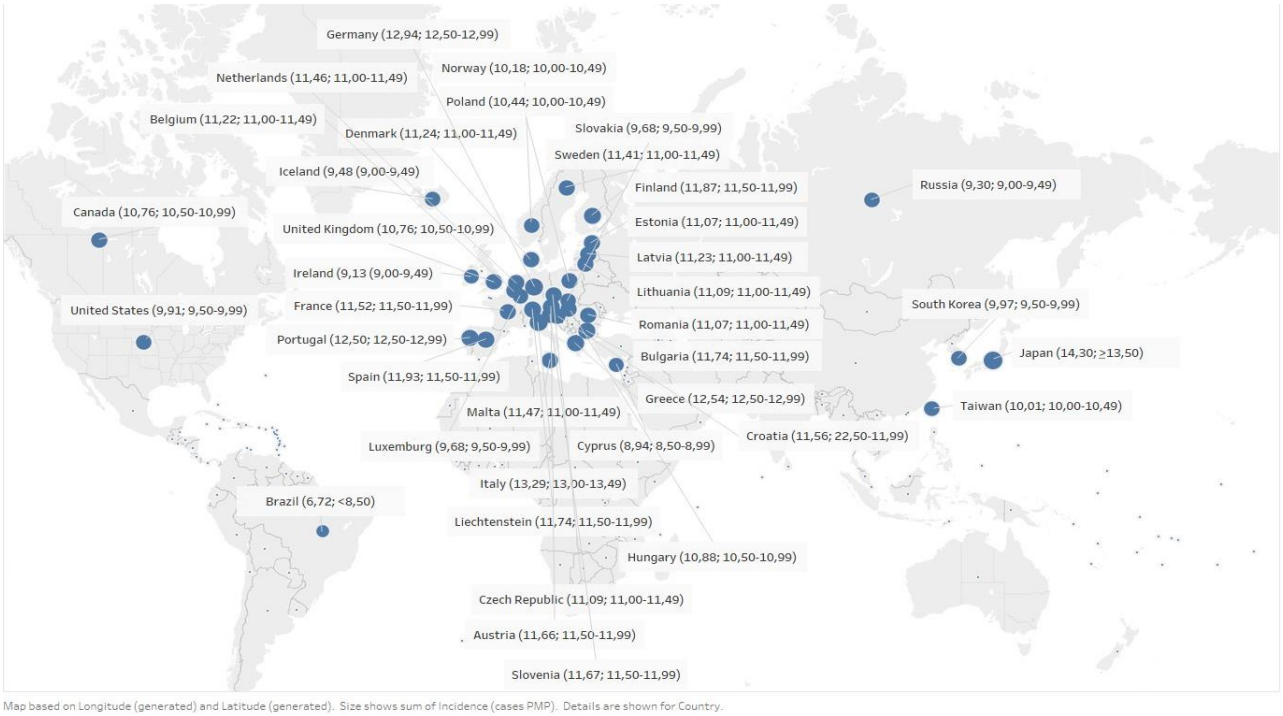


Figure 7[18]

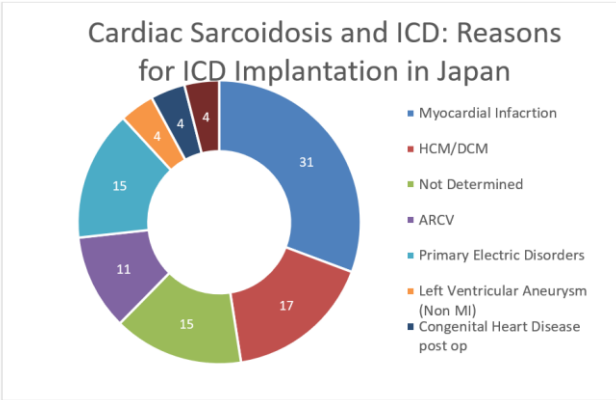


Figure 8. [20]

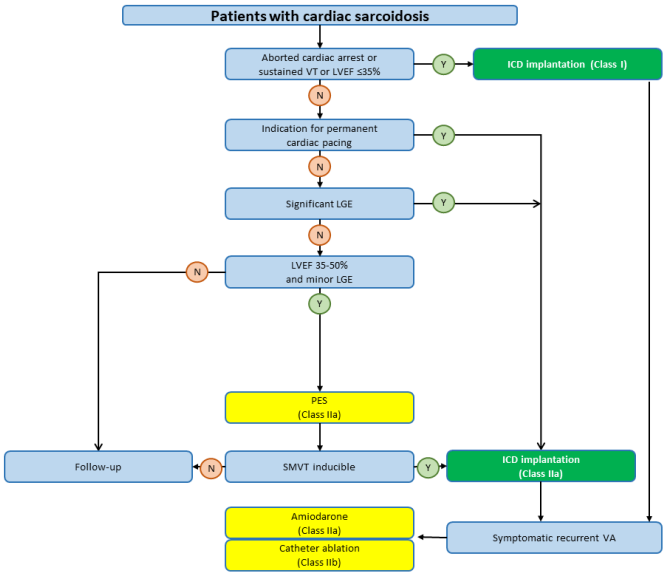


Figure 9.[11]

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Disclosures and Ethics

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Platelet Activation Pathway in Guiding Antiplatelet Therapy on Cardiovascular Disease (CVD): Is one superior to the others?

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ABSTRACT

Cardiovascular disease (CVD) is a leading cause of death worldwide, with an estimated 31% global death rate and mostly up to 85% resulting from stroke and myocardial infarction. Thrombosis plays a pivotal role in this condition due to "blood clot" initiation that disrupts blood flow and induces an ischemic event. These mechanisms make the platelet activation and aggregation mechanism the focus of study for many years in order to reduce morbidity and mortality related to CVD. The use of antiplatelets to treat CVD is achieved by balancing between ischemic and bleeding events. Several strategies have been established, such as shortening or prolonging dual antiplatelet (DAPT) duration, using single antiplatelet therapy in certain conditions, aspirin-free therapy, and escalating or de-escalating antiplatelet therapy after percutaneous intervention, among others. Hence, it is important to understand the platelet activation pathway to be able to choose the right antiplatelet for the treatment of CVD.

INTISARI

Penyakit kardiovaskular merupakan penyebab utama kematian di seluruh dunia. Diperkirakan sekitar 31% kematian global disebabkan oleh penyakit kardiovaskular terutama stroke dan infark miokard yang mencapai angka 85%. Trombosis berperan penting pada kondisi ini melalui mekanisme pembentukan sumbatan atau jendalan darah yang mengganggu aliran darah sehingga mengakibatkan kejadian iskemik. Kondisi ini menjadikan aktivasi dan agregrasi platelet sebagai fokus studi selama bertahun-tahun dengan tujuan menurunkan angka morbiditas dan mortalitas terkait penyakit kardiovaskular. Penggunaan antiplatelet pada terapi kardiovaskuler dicapai melalui keseimbangan antara kejadian iskemik dan risiko perdarahan. Berbagai strategi telah dikemukakan antara lain memperpendek atau memperpanjang durasi penggunaan dobel antiplatelet, penggunaan antiplatelet tunggal, strategi bebas aspirin, eskalasi dan de-eskalasi antiplatelet paska intervensi perkutan, dsb. Memahami jalur aktivasi platelet penting untuk dilakukan agar klinisi dapat memilih antiplatelet dengan tepat dalam terapi kardiovaskular.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death worldwide, with an estimated 31% global death rate and mostly up to 85% resulting from stroke and myocardial infarction. Thrombosis plays a pivotal role in this condition due to "blood clot" initiation that disrupts blood flow and induces an ischemic event. These mechanisms make the platelet activation and aggregation mechanism the focus of study for many years in order to reduce morbidity and mortality related to CVD. The use of antiplatelets to treat CVD is achieved by balancing between ischemic and bleeding events. Several strategies have been established, such as shortening or prolonging dual antiplatelet (DAPT) duration, using single antiplatelet therapy in certain conditions, aspirin-free therapy, and escalating or de-escalating antiplatelet therapy after percutaneous intervention, among others. Hence, it is important to understand the platelet activation pathway to be able to choose the right antiplatelet for the treatment of CVD.

Platelet Activation Pathway

Platelets are the major cellular components of the hemostatic system, aiming to minimize blood loss by forming a hemostatic plug along with crosslinked fibrin after vascular injury. Physiologically, the vascular endothelium plays a crucial role in preventing platelet activation through various mechanisms. It releases nitric oxide (NO) and prostaglandin I2 (PGI2, also known as prostacyclin), which discourage platelet activation. Additionally, it expresses ectonucleotidases that break down adenosine triphosphate (ATP) and adenosine diphosphate (ADP), leading to the generation of adenosine. Moreover, the endothelium expresses thrombomodulin, which binds to thrombin and counteracts its prothrombotic effects. PGI2 and NO activate adenylyl and guanylyl cyclases within platelets, resulting in increased levels of intraplatelet cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP). These cyclic nucleotides activate protein kinases (PKA and PKG), leading to the phosphorylation of specific substrates, thereby interfering with their synthesis. The accumulation of cAMP and cGMP also hampers signals initiated by platelet receptor agonists, which in turn disrupts the elevation of cytosolic calcium (Ca2+) and the reorganization of the cytoskeleton. In order to maintain proper regulation, three phosphodiesterase (PDE) isoforms (PDE2, PDE3, and PDE5) play a vital role by catalyzing the hydrolysis of cAMP and cGMP into inactive 5'-AMP and 5'-GMP. This enzymatic action limits the intracellular levels of cyclic nucleotides, ensuring precise control over platelet activation.[1]

When vascular injury happens, a series of events occur involving platelets. Initially, platelets roll along the sub-endothelial surface through an interaction between the integrin known as GPIb-V-IX and von Willebrand factor (VWF). This rolling action stabilizes platelets as they adhere to VWF via the second receptor GPIIbIIIa, as well as the collagen receptors GPIaIIa and GPVI. These receptor interactions trigger a cascade of intracellular events. Phosphoinositide 3-kinase (PI3K) and phospholipase C gamma (PLCγ) are activated, leading to the release of calcium ions (Ca2+) into the cytoplasm. Calcium ions, in conjunction with protein kinase activity, activate cytosolic phospholipase A2 (PLA2) within the activated platelets. PLA2 then facilitates the synthesis and secretion of thromboxane A2 (TXA2) by releasing arachidonic acid (AA). Thromboxane A2 (TXA2) is generated from arachidonic acid (AA) through a sequential process involving cyclooxygenase-1 (COX-1) and TXA2 synthase. TXA2 serves a dual role as both a platelet activator and a potent vasoconstrictor. It activates platelets in an autocrine (self-stimulation) and paracrine (stimulation of nearby cells) manner through its interaction with the thromboxane receptor (TP). Additionally, TXA2 contributes to vasoconstriction, further influencing vascular function.[1] Human platelets possess three types of granule storage compartments: α-granules, dense granules, and lysosomes. Among these, dense granules contain small molecules such as ADP, ATP, serotonin, calcium ions (Ca2+), pyrophosphate, and polyphosphate, among others. Upon activation, platelets release the contents of these granules, which act as soluble agonists that bind to purinergic receptors, specifically P2Y1 and P2Y12. P2Y1 is responsible for regulating platelet shape changes and inducing an initial, weak, and transient phase of aggregation. On the other hand, P2Y12 activation inhibits Gαi adenylate cyclase-mediated signaling, leading to a decrease in cyclic adenosine monophosphate (cAMP) levels. This reduction in cAMP levels activates various downstream substrate proteins, ultimately resulting in platelet activation. The activation of platelets triggers a conformational change in GPIIbIIIa, a platelet receptor, transitioning it from a low-affinity state to a high-affinity state for molecules such as fibrinogen, von Willebrand factor (VWF), and fibronectin. This change facilitates platelet aggregation and further activation. Activated platelets play a multifaceted role, as they release growth factors, chemokines, and coagulation factors. Additionally, they interact with leukocytes and the coagulation system, mediating a process known as thrombo-inflammation. This intricate interplay is critical in the regulation of hemostasis and inflammatory responses within the body.[1]

CONCLUSION

Metabolic syndrome is prevalent in patients with heart failure. Metabolic syndrome increases the risk of developing heart failure. In contrast, heart failure with metabolic syndrome is linked to a specific pathophysiological process, namely obesity and chronic inflammation state link metabolic syndrome and heart failure. Metabolic syndrome and heart failure are associated with increased concentration of biomarkers and activation of pathways related to lipid metabolism, obesity, and chronic inflammation.

Antiplatelet Targeted Therapy

Soluble agonists like ADP and thromboxane A2 (TxA2) play a central role in driving thrombus development, making them the target of antiplatelet therapy. ADP released from damaged endothelial cells and activated platelets acts on P2Y1 and P2Y12, inducing further platelet activation and the release of ADP. The TxA2 produced and released by stimulated platelets also activates additional platelets, thereby promoting plug formation.[2] Aspirin, the first antiplatelet drug, works by irreversibly blocking the platelet-induced cyclooxygenase (Cox)-1 enzyme to inhibit the formation of TxA2, which acts as an effective agonist of platelet aggregation and vasoconstrictor. Other antiplatelet agents are P2Y12 receptor antagonists, including thiophene pyridines (clopidogrel and prasugrel) and non-thiophene pyridines (ticagrelor). Thienopyridines are oral pro-drugs that require hepatic activation via cytochrome P450, and their metabolites irreversibly bind to P2Y12 receptors for 7 – 10 days. In contrast, non-thienopyridines are potent, reversible, and direct-acting drugs. Besides their antiplatelet action, ticagrelor has additional effects that some studies have referred to as "superior" to others, such as increasing adenosine plasma concentration, leading to an increase in adenosine-related coronary blood flow, providing cardio-protection, and also promoting the release of anticoagulative factors.[3]

Balancing Between Ischemic and Bleeding Risk

The 2020 European Society of Cardiology (ESC) Guidelines for the Management of Acute Coronary Syndrome in Patients Presenting without Persistent ST-elevation Myocardial Infarction stated that both ischemic and bleeding complications will significantly influence the outcome of NSTE-ACS patients and their overall risk of mortality. Therefore, the choice of treatment should equally take both into consideration.[4]

Choosing the antiplatelet after PCI

According to the 2020 ESC NSTE-ACS Guidelines, dual-antiplatelet therapy (DAPT) consisting of a potent P2Y12 inhibitor in addition to aspirin is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications. The duration of DAPT can be shortened (<12 months), extended (>12 months), or modified (by switching DAPT or de-escalation) in specific clinical scenarios. These decisions should be made based on clinical judgment driven by the patient's ischemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medication, and the availability of respective drugs.[4]

A study by Khan et al. (2020) showed that extended-term DAPT (>12 months) was associated with a higher risk of major bleeding compared to 12-month DAPT. Short-term DAPT (<6 months) followed by P2Y12 inhibitor monotherapy was associated with a lower risk of major bleeding. Both mid-term DAPT (6 months) and short-term DAPT followed by aspirin monotherapy showed no significant difference in major bleeding risk compared to 12-month DAPT. Compared to extended-term DAPT, 12-month DAPT, mid-term DAPT, and short-term DAPT followed by aspirin or P2Y12 inhibitor monotherapy were associated with a reduced risk of major bleeding.[5]

In comparison with 12-month DAPT, extended-term DAPT was associated with a reduced risk of MI, whereas midterm DAPT, short-term DAPT followed by aspirin monotherapy or P2Y12 inhibitor monotherapy showed no significant differences. A higher risk of MI was significantly associated with 12-month DAPT, midterm DAPT, and short-term DAPT followed by aspirin monotherapy or P2Y12 monotherapy compared to extended-term DAPT.[5]

Regarding definite or probable stent thrombosis, extended-term DAPT reduced the risk compared to 12-month DAPT. Interestingly, short-term DAPT followed by aspirin was associated with a higher risk of definite or probable stent thrombosis compared to extended-term DAPT, 12-month DAPT, and midterm DAPT. However, this effect was not observed with the use of short-term DAPT followed by P2Y12 inhibitor monotherapy.[5]

Previous studies and meta-analyses comparing guided versus standard antiplatelet therapy in patients with high on-treatment platelet reactivity (HBR) or carriers of CYP2C19 loss-of-function alleles, which are associated with increased thrombotic risk, have shown that a guided approach was associated with a reduction in cardiovascular death, myocardial infarction, stent thrombosis, and stroke, but there was no difference in all-cause death. Compared to standard therapy, a guided approach was associated with a reduction in minor bleeding but not major bleeding.[6]

Strategies for reduced bleeding risk

Shortening DAPT

After PCI procedure, in patients with moderate or high bleeding risk, DAPT can be shortened to either 1 month when followed by clopidogrel monotherapy or to 3 months in NSTE-ACS and 6 months in STE-ACS when followed by aspirin monotherapy. Clopidogrel should be preferred over potent P2Y12 inhibitors in this population.[7]

P2Y12 monotherapy

he NSTE-ACS guidelines introduce the use of ticagrelor monotherapy three months after PCI among patients at low ischemic risk.[7] The TWILIGHT-ACS study reported an advantage of ticagrelor monotherapy initiated after three months of combined therapy with aspirin, compared to standard DAPT (i.e., 12 months of ticagrelor and aspirin), in reducing the incidence of clinically relevant bleeding events in patients at high risk of bleeding or ischemic events undergoing drug-eluting stent (DES) implantation. Moreover, the TICO trial demonstrated that in ACS patients treated with DES, ticagrelor monotherapy after three months of DAPT resulted in a reduction in the composite outcome of major bleeding and cardiovascular events at one year, compared to ticagrelor-based 12-month DAPT.[3]

De-escalation of DAPT

Switching from potent drugs like prasugrel or ticagrelor to clopidogrel in NSTE-ACS patients may be considered as an alternative regimen in treatment. However, it is important to note that there is a potential for increased ischemic risk with a uniform de-escalation of P2Y12 receptor inhibitor therapy after PCI, especially if performed early (<30 days) after the index event. De-escalation may be considered if there is a high bleeding risk. NSTE-ACS Guidelines also state that de-escalation guided by either platelet function testing or CYP2C19-directed genotyping may be considered in selected patients as an alternative to 12 months of potent platelet inhibition, especially for patients who are not suitable for this therapy strategy.[4]

All of these strategies must be chosen based on each patient's characteristics, including ischemic and bleeding risk, comorbidities, and adverse events. Data from the Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients (PARIS) registry suggests that physician-guided discontinuation of DAPT is safe and not associated with an increased risk of major adverse cardiac events. These findings support the customization of DAPT therapy according to individual patient characteristics.[3]

Conclusion

The choice of the appropriate antiplatelet therapy should be tailored by clinicians to match each patient's specific condition, taking into account factors such as the underlying disease, bleeding risk, and comorbidities.

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