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Editorial

The Importance of Managing HbA1c in Coronary Artery Disease: Keep It Low

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ABSTRACT

Coronary Artery Disease (CAD) is the most prevalent cardiovascular disease, which remains the leading cause of death worldwide. In Indonesia, it accounts for approximately 1.5% of the entire population. Diabetes mellitus (DM) is taken into consideration as one of the most potent risk factors for cardiovascular diseases. Haemoglobin A1c (HbA1c) reflects a long-term glycemic control and is used as a valuable diabetes biomarker. High serum glucose levels, expressed as glycated hemoglobin levels in diabetics or non-diabetics, are related to varying degrees of systemic inflammation and promote the release of the proinflammatory cytokines. The association between higher glycated serum HbA1c levels and the severity of the coronary disease is well known. The predictive value of HbA1c for CAD severity, re-hospitalization, and the mortality of cardiovascular disease had been studied extensively since 2004. Numerous previous trials discovered that severity of CAD correlated with the elevation of HbA1c levels, suggesting it as a broad surrogate marker for CAD. Thus, HbA1c is currently considered as an independent risk factor for CAD. A higher level of HbA1c and the presence of factors associated with ongoing atherosclerosis and extensive CAD are concomitantly contributing to the higher major adverse cardiovascular events (MACEs) incidence and long-term mortality.

Coronary Artery Disease (CAD) is still the leading cause of death of non-communicable diseases worldwide. CAD refers to the pathologic process of atherosclerosis affecting the coronary arteries. It remains predicted to be the leading cause of death globally within the next 15 years, particularly in developing countries.1 Indonesia is one of the developing countries with a high prevalence of CAD regarding data from Riskesdas (2018), conducted by the Ministry of Health Republic of Indonesia, with an estimation of 1.5% prevalence of the Indonesian population.[2]

Diabetes mellitus (DM) is taken into consideration as one of the major potential risk factors for cardiovascular disease. Compared to non-diabetes of the same sex, age, and ethnicity, the excess risk for cardiovascular disease was found to be two to eight times higher in patients with diabetes mellitus.[3] Glucotoxicity and lipotoxicity leading to prolonged hyperglycemia and the dysfunction of beta-cell are reversible early pathophysiological events. This suggests that the course of hyperglycemia and prevent or delay long-term complications can be changed by proper management.[4]

Hemoglobin A1c (HbA1c) indicates long-term glycemic control, which also tracks well in individuals over time, in comparison to fasting glucose specifically. In diabetics, HbA1c is associated with microvascular disease development and is central to hyperglycemia's clinical management. Even though there is evidence that HbA1c levels are also related to macrovascular disease in people with diabetes, this association remains controversial.[5,6] Vascular complications can develop in patients with HbA1c <7.0% and even in undiagnosed patients because of a transient increase in plasma glucose concentration. Macrovascular complications may develop early and do not linearly correlate to HbA1c, as well as microvascular complications. It appears that chronic hyperglycemia is significant in CAD pathogenesis and would extend to individuals with the elevation of HbA1c levels even without a diabetes diagnosis.[4]

HbA1c is a valuable diabetes biomarker used worldwide. Mendel's randomization found genetic evidence that HbA1c is a risk factor for CAD representing two different etiologic pathways, glycemic and erythrocytic. The ability of HbA1c to predict CAD risk likely goes

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beyond its reflection of ambient glycemia and suggests the importance of further research into the biology underlying the HbA1c-CAD association.[6] High serum glucose levels expressed in glycated hemoglobin levels in diabetic or non-diabetic individuals are related with varying degrees of systemic inflammation and promotes the release of the proinflammatory cytokines. The relation between higher glycated hemoglobin levels in the blood with coronary disease severity and hospital admission was associated with low-grade vascular inflammation and long-term promotion of atherogenesis.[7]

Selvin et al. (2005) showed that the elevation of HbA1c levels was an independent risk factor for CAD in people with and without diabetes.[5] Glycosylated HbA1c is an important biomarker that considers fasting and postprandial plasma glucose concentrations over the previous 2-3 months.[3,8] HbA1c has been taken into consideration as the standard criterion for monitoring and diagnosing diabetes mellitus (DM) for many years. It has several advantages over oral glucose tolerance tests and fasting plasma glucose, including greater comfort, greater pre-analysis stability, and less daily distraction during stress and illness. HbA1c has been recommended by The American Diabetes Association (2019) as the most effective diagnostic and prognostic tool for DM and its complications.[9] Selvin et al. (2005) shows that even CAD risk could start at HbA1c less than 7%, the usual target for good glycemic control. Thus, well into the "normal" range (i.e., between 4.6% and 6.0%), HbA1c values relate to CAD. The current study provides guidance on the informative range of HbA1c for CAD risk and suggests that future studies of HbA1c and cardiovascular risk in non-diabetic individuals should be considered.[5] Since 2004, the predictive value of HbA1c for the severity of CAD and cardiovascular mortality in non-diabetes has been extensively studied. Elevation of HbA1c levels was found in many trials to be related with CAD severity, indicating it as an extensive marker of CAD.[3]

Based on research by Timmer and Pai on non-diabetic adults, the Atherosclerosis Risk In Communities (ARIC) study (2015), a higher HbA1c level was related to higher cardiovascular disease and mortality.[6,9] Ghaffari et al. (2015), which evaluate the correlation of HbA1c with CAD severity using the Califf scoring system in STEMI patients, demonstrated similar results as well. Levels of HbA1c on admission correlated with short-term and in-hospital outcomes of non-diabetic patients presenting with STEMI. This study showed HbA1c level > 5.8% in non-diabetic patients with STEMI was related to severe CAD and the involvement of coronary artery multivessel as well. Although the same complications and mortality occurred during the hospitalization period, the significant decrease of 1 year survival in patients with HbA1c level > 5.8% was observed. Among these cases, the percentage of cardiovascular disease-related re-hospitalization was also higher than the HbA1c percentage below the median value.[7]

A meta-analysis conducted by Geng et al. (2017) demonstrated an association between elevated HbA1c level and higher long-term mortality (shown in Figure 1) and higher re-infarction incidence (shown in Figure 2). HbA1c 5.7% to 6.5% is considered prediabetes, according to the most recent guidelines for the diagnosis of diabetes mellitus. In this meta-analysis, eight studies presented the HbA1c threshold of 5.7%, and subgroup analysis of HbA1c levels showed a significant association between prediabetes and long-term mortality. (OR 1.31, 95% CI 1.10–1.55).[10]

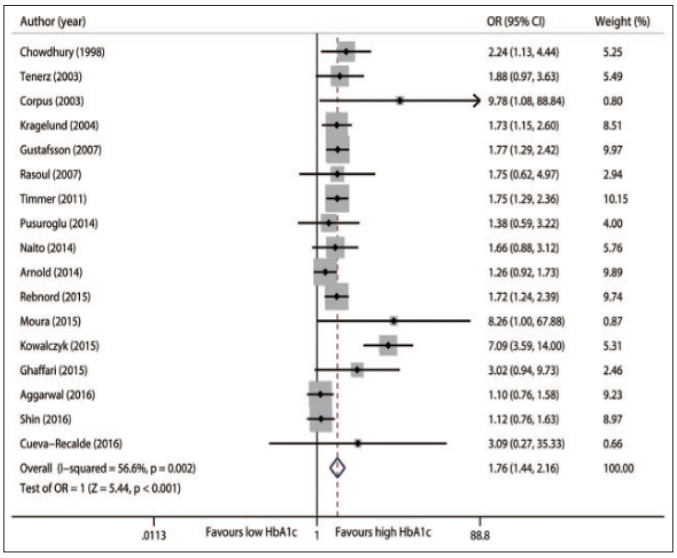

Figure 1. Forest Plot For Long-Term Mortality.[10]

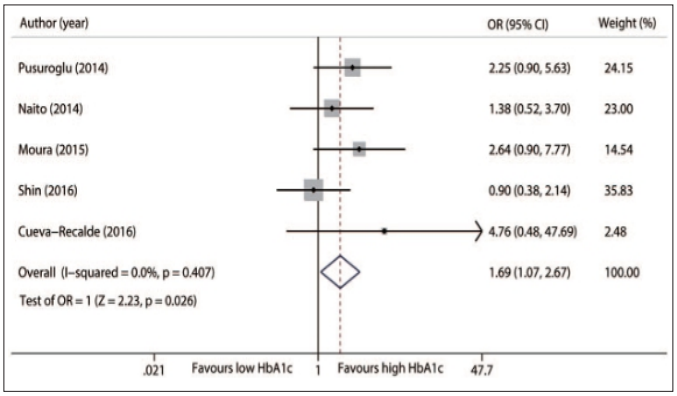

Figure 2. Forest Plot For Re-infarction During Follow-Up.[10]

In conclusion, many data support the involvement of HbA1c as an independent risk factor for CAD. A significant correlation was shown between HbA1c, admission to hospital, coronary artery severity, and adverse cardiovascular events, which could act as a surrogate for worse long-term outcomes. Therefore, it is recommended that HbA1c levels be maintained within normal limits (below 5.7%). Higher HbA1c levels and the presence of factors such as changes in blood glucose levels can be associated with ongoing atherosclerosis and extensive CAD, and together can lead to higher long-term mortality.

Conflict of interest

There is no conflict of interest.

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