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The Relationship of Apolipoprotein B and Major Adverse Cardiovascular Events (MACE) in Patients with Coronary Heart Disease as a Prognostic Factor: A Literature Review

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ABSTRACT

Background: All lipoproteins containing Apo-B contribute to the risk of major adverse cardiovascular events (MACE). Although low-density lipoprotein cholesterol (LDL-C) is the most common marker to assess the risk associated with dyslipidemia, Apo-B levels reflect excess atherosclerotic risk and proatherogenic shifts in lipoprotein, predict the risk of incidental atherosclerotic cardiovascular disease, MACE following ACS, including mortality compared to LDL-C. **Objectives:** This review is held to examine the clear association between Apo-B with MACE in patients with coronary heart disease. **Methods:** Studies examining the relationship between Apo-B and MACE in coronary heart disease published in 2018-2023 are searched comprehensively using advanced search on PubMed, Google Scholar, and Cochrane. The relevant studies in Indonesian or English are included and qualitatively reviewed. **Result and Discussion:** There are 17,392 studies identified, four of which meet the inclusion criteria and have low risks of bias in most domains. Study indicates Apo-B levels are significantly associated with the long-term risk of MACEs, especially in patients with comorbidities. After primary PCI, high Apo-B levels predict a greater and significant incidence of MACE compared to LDL-C and non-HDL-C. Apo-B reduction also triggers a significant decrease in MACE, unlike non-HDL-C control. Hence, lipid therapy after ACS should focus on Apo-B. Low Apo-B correlates with malnutrition, old age, comorbidities thus indicating a worse prognosis for ACS. Therefore, identification of comorbidities should be considered. **Conclusion:** This review provides strong evidence that Apo-B level has better prognostic information of MACE following coronary heart disease, especially in patients with comorbidities, compared to other lipid profiles. Therefore, controlled Apo-B is preferred as a therapy target.
Keyword: Apo-B, coronary, heart, MACE, prognosis

ABSTRAK

Latar Belakang: Semua lipoprotein yang mengandung Apo-B berkontribusi terhadap risiko kejadian kardiovaskular utama yang merugikan (MACE). Meskipun kolesterol lipoprotein densitas rendah (LDL-C) adalah penanda yang paling umum digunakan untuk menilai risiko yang terkait dengan dislipidemia, kadar Apo-B mencerminkan risiko aterosklerotik berlebih dan pergeseran proaterogenik dalam lipoprotein, memprediksi risiko penyakit kardiovaskular aterosklerotik insidental, MACE setelah sindrom koroner akut (ACS), termasuk kematian dibandingkan dengan LDL-C. **Tujuan:** Tinjauan ini bertujuan menelaah hubungan yang jelas antara Apo-B dengan MACE pada pasien dengan penyakit jantung koroner. **Metode:** Studi yang meneliti hubungan Apo-B dengan MACE pada pasien penyakit jantung koroner dan dipublikasikan pada 2018-2023 dicari secara komprehensif menggunakan metode pencarian lanjut di Pubmed, Google Scholar, dan Cochrane. Studi yang relevan dalam bahasa Indonesia atau Inggris diinklusi dan ditelaah secara kualitatif. **Pembahasan:** Dari 17.392 studi yang teridentifikasi, sebanyak 4 studi sesuai dengan kriteria inklusi serta memiliki risiko bias rendah pada mayoritas domain. Studi menunjukkan bahwa kadar Apo-B secara signifikan berhubungan dengan risiko MACE jangka panjang, terutama pada pasien dengan komorbiditas. Setelah PCI primer, kadar Apo-B tinggi

memprediksi insiden MACE yang lebih besar dan signifikan dibandingkan LDL-C dan non-HDL-C. Penurunan Apo-B memicu penurunan MACE signifikan, berbeda dengan non-HDL-C. Oleh karena itu, terapi lipid setelah ACS sebaiknya berfokus pada Apo-B. Kadar Apo-B rendah berkorelasi dengan malnutrisi, usia tua, komorbiditas sehingga menunjukkan prognosis yang lebih buruk untuk ACS. Oleh karena itu, identifikasi komorbiditas dipertimbangkan. **Kesimpulan**: Telaah ini memberikan bukti kuat bahwa kadar Apo-B menyediakan informasi prognostik MACE lebih baik setelah penyakit jantung koroner, terutama pada pasien dengan komorbiditas, dibandingkan dengan profil lipid lainnya. Oleh karena itu, pengendalian Apo-B lebih dipilih sebagai target terapi.
Kata Kunci: Apo-B, jantung, koroner, MACE, prognosis

1. Introduction

Several biological markers such as lipid profiles have been used to predict and assess risks of cardiovascular related events in order to manage and prevent further cardiovascular incidence complications. Different lipid subtypes provide different prognostic values, with the most common parameters, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride are prone to being less sensitive. A specific subtype, apolipoprotein B (Apo-B), currently assumed as a more sensitive and reliable marker, is a key structural component of lipoprotein particles synthesized in the liver, such as low-density lipoprotein (LDL), lipoprotein(a), and triglyceride-rich lipoproteins. Apo-B facilitates and strengthens the transfer of cholesterol in a continuous cycle from the liver to peripheral tissues and accurate estimation of Apo-B concentration in serum reflects the burden of atherogenic lipoprotein particles.[1,2]

Low-density lipoprotein cholesterol (LDL-C) is the most commonly used clinical marker to assess the risk associated with dyslipidemia, such as atherosclerotic cardiovascular diseases, including acute coronary syndrome (ACS).[1,3] In patients with acute coronary syndrome (ACS), this risk is managed with statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Statins and ezetimibe reduce circulating LDL-C levels, while PCSK9 inhibitors lower all three types of Apo-B.[1]

However, all lipoproteins containing Apo-B may contribute to the risk of major adverse cardiovascular events (MACE), including but not limited to myocardial infarction, coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), new-onset heart failure, hospitalization due to angina, suspected ischemic stroke, and cardiac death.[2,4] Under physiological conditions, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and lipoprotein A (LpA) particles each contain one Apo-B molecule, allowing Apo-B levels to represent the number of atherogenic particles in the plasma directly contributing to the assessment of atherosclerotic cardiovascular disease risk. In some pathological conditions, LDL-C levels may remain normal with elevated Apo-B, indicating an increase in small, dense LDL particles in the blood. When Apo-B levels do not correspond to non–HDL-C or LDL-C (cholesterol-enriched or cholesterol-deficient Apo-B particles), attention should not solely focus on LDL-C or non–HDL-C levels, as Apo-B becomes a more reliable factor given its accuracy in predicting cardiovascular risk.[1]

Based on recent epidemiological data and clinical studies, in patients with cardiovascular risk factors or stable cardiovascular disease, Apo-B levels provide additional prognostic information about the risk of incidental atherosclerotic cardiovascular disease, MACE, and other risks following ACS, including better prediction of mortality compared to LDL-C alone.[1,2] Secondary prevention studies also report that early Apo-B levels significantly better reflect excess atherosclerotic risk and proatherogenic shifts in lipoprotein composition not captured by LDL-C levels. This is observed in predicting recurrent cardiovascular events in type 2 diabetes mellitus, obesity, metabolic syndrome, and mild to moderate hypertriglyceridemia.[3,4] A meta-analysis study also indicates that reducing Apo-B levels with statins decreases the incidence of cardiovascular events independent of LDL-C levels.[3]

Although Apo-B levels may predict MACE in coronary heart disease patients better than LDL-C, the clear association between the two is still inconclusive. Therefore, this paper is structured to delve deeper into the relationship of Apo-B, especially with the MACE in patients with coronary heart disease.

2. Method

2.1 Databases

The exposition regarding the relationship between Apo-B and MACE in patients with ACS is based on several studies accessed through the PubMed, Google Scholar, and Cochrane databases and qualitatively reviewed.

2.2 Eligibility Criteria

The inclusion criteria for the reviewed studies were as follows:

1. Literature in English or Indonesian

2. Published between 2018-2023

3. Literature investigating the relationship and impact of Apo-B on MACE as stated in the title and/or abstract

Meanwhile, full-article literature that was inaccessible or paid was excluded.

2.3 Literature Search Strategy and Study Selection

The inclusion criteria for the reviewed studies were as follows:

Literature search in the specified databases used the advanced search feature with the following keyword combinations: "apolipoprotein B" OR "apolipoprotein-B" OR "apo-B" OR "apoB" OR "apo B" AND "acute coronary syndrome" OR "myocardial infarction" OR "cardiovascular disease" AND "prognosis" OR "outcome" and filtered according to the inclusion criteria. The literature search results for each database are as follows:

1. PubMed: using the keyword combination (("apolipoprotein B"[Title/Abstract]) OR ("apolipoprotein-B"[Title/Abstract]) OR (apo-B[Title/Abstract]) OR (apoB[Title/Abstract]) OR ("apo B"[Title/Abstract])) AND (("acute coronary syndrome"[Title/Abstract]) OR ("myocard infarction"[Title/Abstract]) OR ("myocardial infarction"[Title/Abstract]) OR ("cardiovascular disease"[Title/Abstract])) AND ((prognosis[Title/Abstract]) OR (outcome[Title/Abstract])), yielded 63 literature results.

2. Google Scholar: using the keyword combination (“apolipoprotein B” OR “apolipoprotein-B” OR "apo-B" OR "apoB" OR "apo B") AND (“acute coronary syndrome” OR “myocardial infarction” OR “cardiovascular disease”) AND (“prognosis” OR “outcome”), obtained a result of 17,200 studies.

3. Cochrane: using the keyword combination “apolipoprotein B” OR “apolipoprotein-B” OR "apo-B" OR "apoB" OR "apo B" AND “acute coronary syndrome” OR "myocardial infarction" OR “cardiovascular disease” AND “prognosis” OR “outcome”, obtained 129 literature results.

From PubMed, 6 studies with titles and abstracts containing relevant keywords were found. Based on the search on Google Scholar, there were 13 studies with titles and abstracts containing search keywords. Meanwhile, from Cochrane, there were 3 studies with relevant titles and abstracts. Of these 22 studies, 7 studies were duplicates.

After deduplicating the studies, upon further investigation, among 15 studies, 3 studies from PubMed and 7 studies from Google Scholar did not investigate the relationship between Apo-B and the prognosis of ACS or MACE, so they were excluded. Meanwhile, the full text of 1 study from Cochrane was inaccessible. Therefore, the final number of included studies is 4, consisting of 3 studies from PubMed and 1 study from Google Scholar.

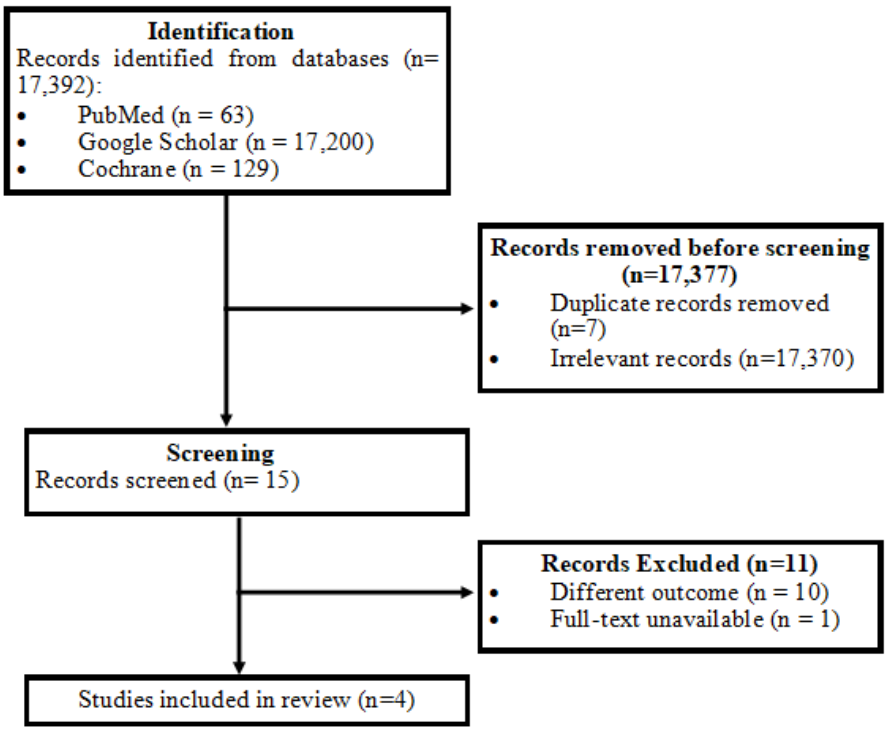

Figure 1. Literature searching algorithm.

3. Result and Discussion

Out of 17,392 studies identified from the three databases, the search process resulted in a total of 4 studies which were finally included in the review. Before being analyzed, each study validity and risk of bias was confirmed to be eligible. Each study investigates the relationship of Apo-B and different aspects of MACE, including MACE in general.

3.1 Apolipoprotein B and MACE

Current studies propose that Apo-B becomes a more reliable cardiovascular events related parameter due to its representation of circulating atherogenic LDL particles. The higher the plasma Apo-B level, the greater the circulating cholesterol concentration thus creating bigger risk of atherosclerotic plaque accumulation. However, this frequency of atherogenic particles, including LDL-C increase, tends to be oxidized, thus making Apo-B a more appropriate marker of cardiovascular risk assessment.

A retrospective study conducted by Zhang et al., 2022, indicates that Apo-B levels are significantly associated with the long-term (>10 years) risk of major adverse cardiovascular events (MACE) with a p-value of 0.002 in all patients with adjusted baseline data (age, gender, risk factors [smoking, hypertension, diabetes mellitus, other lipid levels]) including patients with coronary atherosclerosis and ACS patients with comorbidities such as diabetes mellitus, obesity, and metabolic syndrome. Apo-B has a significantly positive correlation with MACE, especially in patients with obesity, diabetes, or metabolic syndrome. In both groups, Apo-B is an independent risk factor for long-term MACE.[4]

New-onset heart failure is the most frequently occurring MACE significantly associated ($p < 0.001$) with increased Apo-B levels in all subject groups, alongside hospitalization due to angina ($p < 0.001$), myocardial infarction ($p < 0.001$), coronary revascularization ($p= 0.01$), and cardiac death ($p < 0.001$).[4]

Another retrospective cohort study by Ghodsi et al., 2021, examining the relationship between Apo-B and MACE after primary PCI, shows that high Apo-B levels can predict a greater and significant incidence of MACE ($p = 0.036$) compared to LDL-C ($p = 0.077$) and non-HDL-C. Survival from repeat revascularization in subjects with high Apo-B (>65 mg/dl) is lower than in subjects with low Apo-B, with a p-value of 0.041. Meanwhile, non-fatal myocardial infarction shows a less significant positive correlation with Apo-B levels.[2]

Another trial study conducted by Hagström et al., 2022 shows that the incidence of MACE increases proportionally with baseline Apo-B levels in subjects, both before and after adjusting for demographic characteristics and non-lipid clinical variables ($p < 0.0001$).[1]

Therefore, it is suggested that apo B becomes the primary parameter of cardiovascular events risk assessment especially in patients with comorbidities such as obesity, diabetes, or metabolic syndrome whenever available. Moreover, apo B can be examined in a non-fasting condition and is not influenced by variability of triglyceride.

3.2 Apolipoprotein B and Survival Rate

Apo-B is also more accurately associated with long-term survival and MACE assessed through the frequency of myocardial infarction events, hospitalization due to angina, ischemic stroke incidence, or cardiac death, especially in patients with coronary heart disease (CHD). In Zhang *et al*, 2022 article, deep analysis using ROC curves show that in patients with CHD, control of Apo-B is necessary for better long-term survival. The study reports that the relationship of Apo-B with survival rates in patients with coronary atherosclerosis shows a significant inverse correlation with Apo-B levels ($p = 0.003$), while in ACS patients with hypertriglyceridemia, diabetes mellitus, obesity, and metabolic syndrome, the inverse relationship of survival rates with Apo-B levels is proven to be worse with higher incidence of MACE (significance $p = 0.02$; $p = 0.00018$, $p = 0.00091$, and $p < 0.0001$, respectively). The study specifically reports that the survival curve of Apo-B with the level of $\geq$65 mg/dL is lower than in the subjects with Apo-B$\leq$65 mg/dL with p-value = 0.055. Although statistically insignificant, individual quantitative results show more MACEs events.[4]

3.3 Apolipoprotein B versus Other Lipid Profiles and Coronary Atherosclerosis Therapy Recommendation

Several evidences show that Apo B provides mortality risk prediction more accurately than LDL-C or non-HDL-C thus proposed as a target therapy of statin. Apo-B is contained in all lipoproteins attributable to cardiovascular risk assessment (LDL, lipoprotein A, triglycerides). Therefore, controlled Apo-B level is suspected to be more associated with lower risk of MACE compared to measurement of LDL-C and non-HDL-C only.

In a study by Zhang et al, 2022, an analysis was also conducted to assess the strength of each lipid profile in predicting long-term MACE. Based on the analysis results, in normal patients and those with mild coronary atherosclerosis, LDL-C still has a higher predictive value than Apo-B in predicting long-term MACE. However, in ACS patients with obesity, diabetes, or metabolic syndrome, Apo-B has a better predictive value than other lipid profiles. Subjects with LDL-C <1.8 mmol/L or optimal non-HDL-C levels who have Apo-B levels >65 mg/dl have lower survival rates, higher incidences of myocardial infarction, hospitalization, ischemic stroke, and cardiac death compared to subjects with Apo-B <65 mg/dl. Therefore, mainly in ACS patients with comorbidities including diabetes, obesity, or metabolic syndrome, Apo-B control is preferred in maintaining long-term survival compared to non-HDL-C or LDL-C.[4] Ghodsi et al., 2021, also concludes that the target therapy threshold for patients with coronary atherosclerosis is <65 mg/dl for Apo-B.[2]

In Hagström et al, 2022 trial study, subjects treated with a target of Apo-B reduction after 4 months experience a significant decrease in MACE incidence rate across Apo-B strata of $\geq$50 (rate of 4.26 95% CI 3.78-4.79), >35-<50 (rate of 3.09 95% CI, 2.69-3.54), and $\leq$35 mg/dL (rate of 2.41 95% CI, 2.11–2.76) per 100 patient-years, unlike non-HDL-C control, which is less predictive of future MACE occurrences. This suggests that controlling LDL-C and non-HDL-C levels towards optimal values without a concurrent decrease in Apo-B does not guarantee a reduction in the residual risk posed by lipoproteins. Therefore, Hagström et al., 2022 conclude that high-intensity statin therapy and proprotein convertase subtilisin/kexin type 9 inhibitor therapy after ACS should focus on Apo-B as a target, with the preferred target of $\leq$35 mg/dL.[1]

On the other hand, in the retrospective cohort study held by Li et al., 2022, low Apo-B (<65 mg/dl), indicating subjects with baseline characteristics such as malnutrition, old age, comorbidities (hypertension, chronic kidney disease, diabetes mellitus), is associated with a worse prognosis for ACS. However, in models with adjusted covariates, ACS patients with Apo-B <65 mg/dl have a 10% lower risk of long-term death than subjects with Apo-B >65 mg/dl (95% CI: 0.81-0.99). Therefore, lipid management remains a target for preventing MACE in ACS patients, but identification of malnutrition or other comorbidities should also be considered.[5]

The limitations of this study include the lack of systematic review on the collected studies and risk of bias or studies validity assessments. Because most published studies examine the correlation of Apo-B and MACE as observational studies, biases in data analysis are potentially found. In these studies, it is also unclear whether MACEs would be affected by Apo-B dynamic changes. The number of relevant studies are also still limited, so a well-established conclusion applicable for population in general still requires further researches.

However, this literature review has addressed a topic that is still infrequently discussed in the field of health. In reality, the correlation of Apo-B with MACE is an essential condition that, if given more attention and further management, can reduce the risk of MACE and improve the quality of life for patients with heart disease. It is hoped that through this literature review, awareness among healthcare professionals and the general public in controlling risk factors for MACE can be strengthened.

4. Conclusion

The result of the review shows that all lipoproteins containing Apo-B may contribute to the risk of major adverse cardiovascular events (MACE). Current studies mentioned in patients with cardiovascular risk factors or disease, Apo-B levels provide better prognostic information about the risk of MACE following coronary heart disease, especially in patients with comorbidities, compared to other lipid profiles. Therefore, controlled Apo-B is preferred as a therapy target.

5. Recommendations

Further systematic review addressing Apo-B prognostic value on MACEs is preferably held to assess more eligible and qualified studies with broader sample size to be implemented more widely in general population.

References

[1] Hagström E, Steg PG, Szarek M, Bhatt DL, Bittner VA, Danchin N, et al. Apolipoprotein B, Residual Cardiovascular Risk After Acute Coronary Syndrome, and Effects of Alirocumab. Circulation 2022;146(9):657–72.

[2] Ghodsi S, Mohebi M, Sadre-Bafghi SA, Poorhosseini H, Salarifar M, Alidoosti M, et al. Prognostic implications of calculated Apo-lipoprotein B in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: Outcome is tied to lower cut-points. Clin Cardiol 2021;44(6):824–32.

[3] Kawahara H, Endo A, Uchida K, Tanabe K. Prognostic role of apolipoproteins on long-term major adverse cardiac events after percutaneous coronary intervention. Cardiovasc Revascularization Med [Internet] 2023;(August). Available from: https://doi.org/10.1016/j.carrev.2023.10.012

[4] Zhang C, Ni J, Chen Z. Apolipoprotein B Displays Superior Predictive Value Than Other Lipids for Long-Term Prognosis in Coronary Atherosclerosis Patients and Particular Subpopulations: A Retrospective Study. Clin Ther [Internet] 2022;44(8):1071–92. Available from: https://doi.org/10.1016/j.clinthera.2022.06.010

[5] Li H, Wang B, Mai Z, Yu S, Zhou Z, Lu H, et al. Paradoxical Association Between Baseline Apolipoprotein B and Prognosis in Coronary Artery Disease: A 36,460 Chinese Cohort Study. Front Cardiovasc Med 2022;9(January):1–10.