Peran Faktor Genetik dan Epigenetik Terkait Resistensi Klopidogrel terhadap Kejadian Kardiovaskular Mayor pada Pasien Sindrom Koroner Akut Pasca Intervensi Koroner Perkutan = The Role of Genetic and Epigenetic Factors Related to Clopidogrel Resistance in Major Adverse Cardiovascular Events on Acute Coronary Syndrome Patients after Percutaneous Coronary Intervention

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Abstrak

Sindrom koroner akut (SKA) merupakan masalah kesehatan nasional karena tingginya angka morbiditas dan mortalitas serta beban biaya yang dibutuhkan. Intervensi koroner perkutan (IKP) dan terapi antiplatelet seperti klopidogrel merupakan tata laksana yang direkomendasikan oleh organisasi kardiologi internasional. Meskipun demikian, pasien SKA masih dapat mengalami kejadian kardiovaskular mayor (KKM). Kemungkinan, resistensi klopidogrel berperan pada KKM sedangkan resistensi klopidogrel mungkin dipengaruhi oleh faktor genetik dan epigenetik. Penelitian ini bertujuan untuk mengetahui hubungan faktor genetik yaitu polimorfisme gen CYP2C19 dan P2Y12, serta epigenetik yaitu metilasi DNA gen CYP2C19 dan P2Y12 serta ekspresi miRNA-26a dengan resistensi klopidogrel dan pengaruhnya terhadap KKM pada pasien SKA pasca IKP.

Untuk menganalisis hubungan faktor genetik dan epigenetik dengan resistensi klopidogrel, penelitian dilakukan dengan desain potong lintang, sedangkan untuk analisis hubungan faktor genetik dan epigenetik dengan KKM dilakukan dengan desain kohort prospektif. Subjek penelitian meliputi 201 pasien SKA pasca IKP dan mendapat terapi klopidogrel di Rumah Sakit Jantung dan Pembuluh Darah Harapan Kita dari bulan September 2018 sampai dengan Juni 2020. Resistensi klopidogrel ditentukan dengan pemeriksaan light transmission aggregometry (LTA) apabila hasilnya lebih besar dari 59% dengan agonis ADP 20 mM. Deteksi polimorfisme gen CYP2C19 dan P2Y12 serta ekspresi miRNA-26a dilakukan dengan metode qRT-PCR, sedangkan metilasi DNA gen CYP2C19 dan P2Y12 dikerjakan dengan metode konversi bisulfit. Pasien diobservasi selama satu tahun dan jika ada angina pektoris, infark miokard akut (IMA) rekuren, stroke, atau kematian, dicatat sebagai KKM.

Dari 201 subjek, terdapat 45,8% carrier mutant polimorfisme *2 dan *3 gen CYP2C19, 36,8% carrier mutant polimorfisme rs3679479 gen P2Y12, 10% hipometilasi DNA gen P2Y12, 80,1% hipometilasi DNA gen CYP2C19, dan 66,2% ekspresi miRNA-26a up regulated. Proporsi resisten klopidogrel adalah 49,8% dan proporsi KKM adalah 14,9% (kematian 7,5%). Terdapat hubungan antara merokok (p = 0,001; OR 0,37 [IK 95%; 0,20–0,68]), hipometilasi DNA gen CYP2C19 (p = 0,037; OR 2,13 [IK 95%; 1,04–4,37]), dan ekspresi miRNA-26a up regulated (p = 0,020; OR 2,03 [IK 95%; 1,12–3,68]) dengan resistensi klopidogrel. Terdapat hubungan antara jenis kelamin perempuan (p = 0,040; HR 2,73 [IK 95%; 1,05–7,14]), usia 60 tahun (p = 0,035; HR 2,17 [IK 95%; 1,06–4,48]), eGFR rendah (p = 0,001; HR 3,29 [IK 95%; 1,59–6,84]), dan polimorfisme *2 dan *3 gen CYP2C19 (p = 0,047; HR 2,12 [IK 95%; 1,01–4,46]) dengan KKM dalam satu tahun.

Hanya faktor epigenetik berupa metilasi DNA gen CYP2C19 dan ekspresi miRNA-26a yang berhubungan

dengan resistensi klopidogrel. Walaupun resistensi klopidogrel tidak berhubungan dengan KKM, terdapat hubungan antara faktor genetik polimorfisme *2 dan *3 gen CYP2C19 dengan KKM.
.....Acute coronary syndrome (ACS) is a national health problem due to high morbidity and mortality, and cost burden as well. Percutaneous coronary intervention (PCI) and antiplatelet therapy such as clopidogrel are recommended. However, ACS patients could still experience major adverse cardiovascular events (MACE). Clopidogrel resistance possibly plays a role in MACE whereas it may be affected by genetic and epigenetic factors. Therefore, the objective of this study was to determine the relationship between genetic factors which are CYP2C19 and P2Y12 polymorphisms, as well as epigenetic factors which are DNA methylation of CYP2C19 and P2Y12, and miRNA-26a expression and their effects on MACE in post-PCI patients.

To analyze the association between genetic and epigenetic factors and clopidogrel resistance, the study design was cross-sectional, while the study design of relationship between genetic and epigenetic factors and MACE was prospective cohort. The subjects were 201 post-PCI ACS patients who received clopidogrel therapy at Harapan Kita Hospital from September 2018 to June 2020. Clopidogrel resistance was determined by light transmission aggregometry (LTA) if the result was greater than 59% with agonist ADP 20 µM. The detection of CYP2C19 and P2Y12 gene polymorphisms and miRNA-26a expression were carried out by qRT-PCR method, while the DNA methylation of the CYP2C19 and P2Y12 genes were carried out by bisulfite conversion method. Patients were observed for one year and angina pectoris, recurrent acute myocardial infarction (AMI), stroke, or death, were recorded as MACE.

From 201 subjects, 45.8% were CYP2C19*2 and CYP2C19*3 polymorphism mutant carrier, 36.8% were rs3679479 P2Y12 polymorphism mutant carrier, 10% were hypomethylated of P2Y12, 80.1% were hypomethylated of CYP2C19, and 66.2% were up regulated in miRNA-26a expression. 49.8% of subjects were clopidogrel resistant and 14.9% of subjects experienced MACE (death was 7.5%). Smoking (p = 0.001; OR 0.37 [CI 95%; 0.20–0.68]), hypomethylated of CYP2C19 (p = 0.037; OR 2.13 [CI 95%; 1.04–4.37]), and up regulated miRNA-26a expression (p = 0.020; OR 2.03 [CI 95%; 1.12–3.68]) were associated with clopidogrel resistance. Female gender (p = 0.040; HR 2.73 [CI 95%; 1.05–7.14]), age over 60 years old (p = 0.035; HR 2.17 [CI 95%; 1.06–4.48]), low eGFR (p = 0.001; HR 3.29 [CI 95%; 1.59–6.84]), and CYP2C19*2 and CYP2C19*3 polymorphisms (p = 0.047; HR 2.12 [CI 95%; 1.01–4.46]) were associated with MACE in one year.

Only DNA methylation of CYP2C19 and miRNA-26a expression were associated with clopidogrel resistance. Although clopidogrel resistance was not associated with MACE, there was association between CYP2C19*2 and CYP2C19*3 polymorphisms and MACE.