中文題目：發展以基因序列晶片導引之口服抗凝血藥精準處方

英文題目：Development of a gene array guided prescription for direct oral anti-coagulants (DOACs)

作　　者：李振豪[1], 曾大千[2], 劉昱全[3], 王詩涵[4], 林宗憲[5,6], 盧怡旭[5], 邱正安[5], 蔡維中[5,6], 黃天祈[5], 卓士傑[5,6], 吳韋璁[5],李香君[5,6,7]*

服務單位：[1]高雄醫學大學附設中和紀念醫院內科部 [2]國立成功大學生物醫學科技產業學群 [3]高雄醫學大學附設中和紀念醫院臨床試驗中心 [4]高雄醫學大學附設中和紀念醫院藥劑部 [5]高雄醫學大學附設中和紀念醫院內科部心臟內科 [6]高雄醫學大學醫學院醫學系內科 [7]高雄醫學大學醫學院脂質科學暨老化研究中心

Background: Direct oral-anticoagulants (DOACs) have been widely used in clinical conditions such as prevention of stroke and systemic embolism in patients with atrial fibrillation, prevention or treatment of venous thromboemboism including deep vein thrombosis and pulmonary embolism. There are uncommon bleeding side effect and residual thromboembolism risk in DOACs users due to variable predictable or unpredictable factors. The precision prescription of DOACs which can optimize DOACs efficacy with lowest side effects is an unmet clinical need.

Methods: During 2019 Feb to 2021 Sep, individuals with indications for long-term use of DOACs (i.e. apixaban, dabigatran, edoxaban, and rivaroxaban) and those who were also DOACs active users are eligible for enrollment in this cohort study. Axiom Precision Medicine Diversity Array (PMDA) was chosen for determining over 850,000 single Nucleotide Polymorphism (SNP) that are relevant to variable cardiovascular diseases and pharmacogenetic effects. The primary and secondary outcomes include bleeding adverse events which is defined by the Global Utilization of Streptokinase and T-pa for Occluded Arteries (GUSTO) Bleeding criteria, intracranial hemorrhage, and thromboembolism event and any cause of death. The other outcome factors include blood concentrations of DOACs, at the time before and 2 hours after taking the medicine. Genome-wide association study (GWAS), and logistic regression model using the generalized linear model were used for analysis of gene array data.

Results: We currently have enrolled 201 patients using either DOACs, and among those 94 (46.8%) used rivaroxaban, 43 (21.6%) used apixaban, 32 (15.9%) used dabigatran, and 32 (15.9%) used edoxaban. There was no sex difference (66.2% were male and 33.8% were female, P=0.68). Bleeding events had been uncommonly observed with 19 patients (20.2%) in rivaroxaban group, 5 patients (11.6%) in

apixaban group, 5 patients (15.6%) in dabigatran group, and 6 patients (18.8%) in edoxaban group. There was no significant difference in bleeding incidence among DOACs groups (P=0.868). Intracranial hemorrhage had not been reported in our currently enrolled patients. There were wide ranges of blood concentrations of DOACs for before and after drug use (the median, 25^{th}–75^{th} percentile): rivaroxaban, before (41.8, 28.1–88.3 ng/ml) and after (578.6, 453.9–682.9 ng/ml); apixaban, before (83.0, 40.0–146.5 ng/ml) and after (200.4, 149.3–252.6 ng/ml); dabigatran, before (695.1, 362.8–1043.2 ng/ml) and after (978.2, 408.0–1624.7 ng/ml); edoxaban, before (9.8, 7.5–29.0 ng/ml) and after (171.4, 131.7–250.4 ng/ml).

Expected results for GWAS include bleeding and thromboembolism-related SNP, that will be applied to design the customized gene chips for DOACs. The customized DOACs gene array will be tested in a randomized controlled trial with two study groups, one with gene array-guided prescription of DOACs and the other with ordinary physicians decision making on DOACs prescription. Intention-to-treat analysis would be performed.

Conclusion: The application of state-of-the-art genetics technology, we believe, will help physician to achieve a precise prescription of DOACs for every single person. The gene-array guided DOACs prescription that will be developed in this study will become a paradigm for precision medicine in future clinical practice.