ステント留置後の長期抗血小板薬2剤併用療法 (Abstract 19168)

DAPT：抗血小板薬2剤併用療法を薬剤溶出ステント留置後1年以上継続することにより冠動脈血栓のリスクが低下する

DAPT: Continuing dual antiplatelet therapy beyond 1-year after placement of drug-eluting stent reduces risk of coronary thrombosis

チエノピリジン系薬剤（クロピドグレルまたはプラスグレル）およびアスピリンをステント留置後標準的な12か月を超えて内服した患者は標準的な12か月のプロトコールに従って治療された患者よりも、ステント血栓および重大な心血管有害事象のリスクが低い、とのlate-breaking clinical trialの結果が2014年American Heart Association年次集会で発表され、同時に*New England Journal of Medicine*に掲載された。DAPT（抗血小板薬2剤併用療法）スタディは5年間の国際スタディであり、薬剤溶出ステントを留置された患者9,961人（平均年齢62歳、約25%が女性、ほとんどが米国出身）をランダム化し一次解析した。ステント留置後アスピリンとクロピドグレルまたはプラスグレルを12か月ではなく30か月内服した患者は、12か月内服しその後アスピリンとプラセボを18か月間内服した患者（プラセボ群）よりもステント内血栓を発症する確率が0.5倍少なかった。彼らはまたプラセボ群と比較し新たな心筋梗塞を発症するリスクが約半分であった。また、チエノピリジン系薬剤治療中止がいつであってもその後3か月間は虚血イベントが著明に増加することも示され、2剤併用療法はさらに長期にわたり継続すべきであり生涯にわたり継続する必要性さえある可能性が示唆された。

Full Text

Patients who took a thienopyridine drug (clopidogrel or prasugrel) and aspirin beyond the standard 12 months after stent placement reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events than those whose treatment followed the standard 12 month protocol, according to late-breaking clinical trial research presented at the American Heart Association's Scientific Sessions 2014 and simultaneously published in *New England Journal of Medicine*.

"We know that dual antiplatelet therapy is essential for all patients receiving coronary stents to prevent blood clots within the stents (in-stent thrombosis). This study showed that the preventive benefit continues when the medications can be taken for more than one year," said the study's principal investigator and lead author, Laurel for 30 rather than 12 months after stent placement were 0.5 times less likely to develop in-stent thrombosis than patients who received dual therapy for 12 months, followed by aspirin plus placebo for 18 months (placebo group) and had about half the risk of having new myocardial infarctions compared to the placebo group.

"Overall the benefits of longer therapy were very consistent throughout the types of patients we studied, and outweighed the risks," she said.

"The DAPT (Dual Antiplatelet Therapy) Study was the first and only study comparing durations of treatment with antiplatelet therapy that was adequately powered to detect a benefit on stent-related heart attacks," said Mauri, who is an interventional cardiologist at Brigham and Women's Hospital, associate professor of medicine at Harvard Medical School and Chief Scientific Adviser at the Harvard Clinical Research Institute in Boston, Massachusetts.

To prevent blood clots, standard post-stent treatment involves dual treatment with aspirin and another anti-clotting medication. European guidelines call for six to 12 months of this treatment and U.S. guidelines recommend it for 12 months after the procedure. What was unclear until now was whether extending this combined treatment for longer than 12 months could decrease the risk of in-stent thrombosis or whether it would prevent heart attack or stroke. The safety of longer-term treatment was also assessed in this trial.

Although moderate to severe bleeding was more common among the medication group than the placebo group in the study, fatal bleeding was rare among both groups of patients.

Of particular interest, it was found that ischemic-event rates increased markedly in the 3-month period after discontinuing thienopyridine treatment regardless of when that occurred, leading to suggestions that treatment should maybe continue longer, even for life. While overall stroke rates and death rates were not reduced by extending the combined treatment, the investigators noted in a secondary analysis, including data beyond the time point after all patients had stopped the study drug (to 33 months), that death from any cause was 0.8 percent higher (2.3 percent vs. 1.5 percent) among the medication group compared to those on placebo. The study results were tracked during the study by a data safety monitoring committee, but this difference in risk was not evident until the end of the study, Mauri said.

A secondary analysis revealed that the higher death rate was attributable to trauma and cancer.

"However, there was no difference in the occurrence of new cancers," Mauri said. "In retrospect, it appears that there may have been an imbalance between the groups in the number of patients with known cancer before enrollment in the study. Taken together with results from many other large studies of these medications, enrolling over 60,000 subjects worldwide, that show no difference in mortality, it seems likely that this finding was related to a chance imbalance between the groups studied in the trial."

Prevention of heart attack and blood clots in stents with longer antiplatelet therapy was consistent in all patient groups, drug and stent types studied, Mauri noted, but "physicians should consider individual patient risks in prescribing dual anti-clotting therapy. In particular, the trial excluded patients with a history of major bleeding either before the stent procedure or within the first year of treatment."

DAPT was a five-year, international study of 25,682 patients. 22,866 received drug-eluting stents, and of these 9,961 patients (average age 62, about 25 percent female, and mostly from the United States) were randomized in the primary analysis. The investigators randomly assigned patients to one of the two groups, and neither investigators nor patients knew who was receiving medication versus placebo. The study took place from August 2009, to June 2014, at more than 450 sites in the United States, Canada, Europe, Australia, and New Zealand.

Limitations of the study include the fact that it only included patients who were known to have tolerated anti-clotting medication for a year; and follow-up ended after 33 months, even though the study data suggest that a longer course of treatment may provide additional benefit.

The Harvard Clinical Research Institute and the following stent and pharmaceutical companies supported the study: Abbott; Boston Scientific Corporation; Cordis Corporation; Medtronic, Inc.; Bristol-Myers Squibb Company/Sanofi Pharmaceuticals Partnership; Eli Lilly and Company; and Daiichi Sankyo Company Limited.

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