トライアルの結果、長期抗血小板療法の有効性に異議が唱えられた

PRODIGY：ステント留置後24か月のクロピドグレル投与は6か月投与と比較し何ら利点はない

PRODIGY: Twenty-four months of clopidogrel after stenting no better than six months

冠動脈疾患患者に対する長期抗血小板薬投与の有効性および安全性を評価した無作為化多施設オープンラベルスタディの結果、24か月間の抗血小板薬2剤併用療法（DAPT）は6か月の併用療法と比較し、心有害事象予防において好ましいということはないことが示された。ステント誘発性内膜肥厚グレーディング後長期抗血小板薬2剤併用療法スタディ（PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY：PRODIGY）の結果が2011年European Society of Cardiology学会で発表された。待機的、早急または緊急冠動脈形成術施行予定の患者2,000人余りを1：1：1：1の割合で4種類のステント（everolimus溶出ステント、パクリタキセル溶出ステント、zotarolimus溶出ステント、または第3世代のストラットの細いベアメタルステント）のうちのいずれか1つを埋め込まれる群に無作為に割り付けた。30日後に各々のステント群患者がさらに6か月または24か月のDAPT群に無作為に割り付けられた。2か月後の総死亡、非致死性心筋梗塞または脳血管事故の合計は、24か月治療群で10.1%、6か月群で10.0%であった（p=0.91）。死亡、心筋梗塞、脳血管事故およびステント血栓それぞれのリスクは2群間で差がなかった。しかし、長期治療群では一貫して予め規定された出血の定義全てに基づく出血のリスクが高く輸血を必要とすることが多かった。

Full Text

A randomized multicenter open-label study evaluating the efficacy and safety of prolonged antiplatelet therapy in patients with coronary disease found that 24 months' duration of dual therapy is no better than six months dual antiplatelet therapy (DAPT) in preventing adverse cardiac events.

However, the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY) also found a consistently greater risk of hemorrhage in the 24-month dual therapy group according to all prespecified bleeding definitions, including the recently proposed Bleeding Academic Research Consortium classification. The need for transfusion was also increased in the longer treatment group.

The results, said investigator Dr. Marco Valgimigli from the University Hospital of Ferrara, Italy, "question the validity of current guideline recommendations - which were based on registry data - that at least 12 months' dual antiplatelet therapy should be pursued after implantation of a drug-eluting stent.

"While we cannot exclude the possibility that a smaller than previously anticipated benefit may still exist in prolonging therapy with clopidogrel for several months after coronary stenting, our study clearly shows that the benefit to risk ratio of prolonged therapy has been over-emphasized."

The PRODIGY study was a 4-by-2 randomized, three-center open-label clinical trial designed to assess the efficacy and safety of prolonged clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced combination of drug-eluting stents (with various anti-intimal hyperplasia potency and belonging to both first and second generation). Patients were 18 years or older with chronic stable coronary artery disease or acute coronary syndromes, including non-ST-elevation and ST-elevation myocardial infarction.

More than 2000 patients scheduled for elective, urgent or emergency coronary angioplasty were randomly assigned in a 1:1:1:1 fashion to one of four stent types: everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting stent or third-generation thin-strut bare metal stent. Randomization to the four different types, said Dr. Valgimigli, was justified by the different safety profile of each, which was meant to ensure that patients in the two main study groups (six versus 24 month dual antiplatelet therapy) received exactly the same stent types. At 30 days, patients in each stent group were then further randomized to either six or 24 months of dual antiplatelet treatment.

The primary objective of the study was to assess whether 24-month dual antiplatelet treatment, consisting of clopidogrel and aspirin after coronary stenting, was associated with a lower cumulative incidence of all-cause mortality, non-fatal myocardial infarction or cerebrovascular accident (the primary outcome) than six-month dual therapy.

Results showed that the cumulative risk of the primary outcome at two years was 10.1% with the 24-month treatment, and 10.0% with the six-month (HR 0.98; 95% CI 0.74-1.29; P=0.91). The individual risks of death, myocardial infarction, cerebrovascular accident or stent thrombosis did not differ between the two groups.

Among the patients receiving long-term dual antiplatelet therapy, there was a roughly two-fold greater risk of type 5, 3 or 2 bleeding events (HR 2.17, 95% CI 1.44-3.22; p=0.00018) as well as type 5 or 3 bleeding events (HR 1.78, 95% CI 1.02-3.13; p=0.037) according to the Bleeding Academic Research Consortium classification. The risks of TIMI-defined major bleeding and red blood cell transfusion were also increased in the 24-month clopidogrel group.

Commenting on the implications of the results, Dr. Valgimigli said: " While a formal economic analysis will follow, the results of this study have important implications for healthcare expenditure - for this study shows that prolonging therapy with clopidogrel beyond six months is not only associated with no clinical benefit but also with a significant increase in actionable bleeding events requiring re-hospitalizations and multiple diagnostic and therapeutic resources."

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