Prior dual antiplatelet therapy and thrombolysis in acute stroke

Dual antiplatelets and thrombolysis

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Letter to the editor

The available evidence on safety of intravenous thrombolysis (IVT) in acute ischemic stroke patients (AIS) on dual antiplatelet therapy (DAPT) is contradictory[1-4]. In particular, clinicians are uncertain whether to use or refrain from IVT in high risk patients, like those with pre-stroke disability who receive DAPT.

Using data from the prospective Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR), Tsivgoulis et al. recently showed that AIS patients on DAPT had similar rates of symptomatic intracerebral hemorrhage (sICH), poor functional outcome and mortality after IVT compared to AIS patients without antiplatelet therapy (APT).[3] We think that this analysis, despite the use of propensity score matching, has some limitations. First, the analysis excluded patients with pre-stroke disability (pre-stroke modified Rankin Scale 2-5), subjects who are more likely to be on DAPT[5]; second, the dataset had a relatively high percentage of missing data (10.5% missing data on APT status, 27% missing data on 3-month outcome and 7.4% on follow-up neuroimaging).

Aiming to overcome these limitations and to increase evidence about safety of DAPT in IVT, we analysed data from the prospective international Thrombolysis in Ischemic Stroke Patients (TRISP) registry. All AIS patients - independently of pre-stroke disability - were included. Primary outcomes included sICH (ECASS-II-criteria), poor functional outcome (defined as modified Rankin Scale 3-6) and mortality (both at three months). DAPT was defined as any combination of antiplatelet therapy with aspirin, clopidogrel, ticagrelor, prasugrel or dipyridamole. Patients without APT and without anticoagulants (AC) served as the comparison group. We performed logistic regression analyses and calculated odds ratios with 95%

confidence intervals [OR, 95%-CI] with adjustment for potentially outcome-modifying variables.

Among 15'156 IVT-treated stroke patients, 8'433 (55.6%) had no APT and no AC, 5'611 (37.0%) were on single APT, 404 (2.7%) were on DAPT and 708 (4.7%) patients were on AC. Data completeness rate was >93% (missing data on APT: 1.1% [n=182]; 3-month outcome: 3.8% [613]; sICH: 1.4% [218]). The proportion of patients with relevant pre-stroke disability (pre-mRS 3-5) in the DAPT group (10.6%) was significantly higher in comparison to patients without APT (6.0%). Besides, patients on DAPT were older and more often had cardiovascular risk factors than patients without APT. The risk of sICH ($OR_{adjusted}$ 1.29[0.82-2.05]), poor outcome ($OR_{adjusted}$ 0.69[0.34-1.20]), and death ($OR_{adjusted}$ 1.48[0.87-2.54]) did not differ significantly between IVT-treated patients on DAPT and no APT (Table 1).

In line with Tsivgoulis et al., our study strongly supports the evidence of not withholding IVT in AIS-patients on DAPT using a different, large prospective, multicenter and multinational data set. Strengths of our study are the high data completeness and – as a refinement – the clarification that safety of IVT in AIS-patients on DAPT applies also to patients with relevant pre-stroke disability.

Author contribution:

VLA designed/conceptualized the study, collected data, analyzed/interpreted the data, drafted the manuscript.

RS designed/conceptualized the study, revised the manuscript.

STE and HG designed/conceptualized and initiated the study, supervised the study, collected data, analyzed/interpreted the data, revised the manuscript.

All other authors collected data, analyzed/interpreted the data and revised the manuscript.

Potential Conflicts of Interest

Valerian L. Altersberger, Rolf Sturzenegger, Gian Marco De Marchis, Christian Hametner, Anne Berberich, Jan F Scheitz, Sophie A. van den Berg, Stefania Nannoni, Alessandro Pezzini,

Guido Bigliardi, Laura Vandelli, Silja Räty, Kati Valkonen, Nicolas Martinez-Majander, Marjaana Tiainen, Patrik Michel, Kiran M Gopisingh, Davide Strambo, Paul J. Nederkoorn, Mirjam R. Heldner, Solène Moulin, Hebun Erdur, Henrik Gensicke, George Ntaios and Sami Curtze report no relevant disclosures.

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Table 1. Multivariable analysis of outcomes (odds adjusted for variables with p<0.1 in the univariable analysis). Odds ratio (95% confidence interval), p-value.

	Outcome measures		
Putative predicting variables	**sICH**	**Poor outcome**	**Mortality**
Dual antiplatelet vs no APT and no AC	1.29 (0.82-2.05) [1] p=0.272	0.69 (0.34-1.20) [2] p=0.185	1.48 (0.87-2.54) [3] p=0.150

1: adjusted for age, NIHSS, dual antiplatelet
2: adjusted for age, sex, stroke to needle time, NIHSS on admission, relevant pre-stroke disability, atrial fibrillation, diabetes, hypertension, hypercholerserolemia, smoking, coronary artery disease, prior ischemic stroke, RR systolic on admission, glucose on admission, creatinine on admission, dual antiplatelet
3: adjusted for age, NIHSS on admission, relevant pre-stroke disability, atrial fibrillation, glucose on admission, creatinine on admission, dual antiplatelet

Abbreviations:
sICH: symptomatic intracerebral hemorrhage
APT: antiplatelet therapy
DAPT: dual antiplatelet therapy
AC: anticoagulation
NIHSS: National Institutes of Health Stroke Scale