Stefan Russmann[1,2,3,4], Ali Rahmany[1,3,4], David Niedrig[1,5], Karl-Dietrich Hatz[6], Katja Ludin[7], Andrea M. Burden[4], Lars Englberger[8], Roland Backhaus[9], Andreas Serra[2], Markus Béchir[3]

# Implementation and Management Outcomes of Pharmacogenetic CYP2C19 Testing for Clopidogrel Therapy in Clinical Practice

[1] drugsafety.ch, Küsnacht, [2]Institute of Internal Medicine and Nephrology, Clinic Hirslanden, Zurich, [3]Center for Internal Medicine, Clinic Hirslanden, Aarau, [4]Pharmaceutical Sciences, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, [5]Hospital Pharmacy, Clinic Hirslanden, Zurich, [6]Sonogen AG, Zurich, [7]Labor Risch, Mocelular Genetics, Berne, [8]Cardiac Surgery, Clinic Hirslanden, Aarau, [9]Stroke Center and Clinic for Neurology, Clinic Hirslanden, Zurich

## Purpose

The antiplatelet prodrug clopidogrel is bioactivated by the polymorphic enzyme CYP2C19. Prospective clinical studies demonstrated an association between CYP2C19 loss of function (LoF) variants and an increased risk of thrombotic events on clopidogrel, but pharmacogenetic (PGx) testing is not frequently implemented in clinical practice. We report our experience with PGx-guided clopidogrel therapy with particular regard to clinically relevant patient management changes.

## Methods

We conducted a cohort and a nested case-control study analyzing patients that underwent PGx testing for clopidogrel therapy at two Swiss hospitals. Primary outcome was the proportion of patients with clinically relevant PGx-based management recommendations and their implementation. The association of recurrent ischemic events under clopidogrel with CYP2C19 LoF variants and other factors was explored in a multivariate case-control analysis.

## Results

Among 56 patients undergoing PGx testing 18 (32.1%) were classified as CYP2C19 intermediate or poor metabolizers. This resulted in 17 recommendations for a change of antiplatelet therapy, which were implemented in 12 patients (70.1%). In the remaining five patients, specific reasons for non-implementation could be identified. Recurrent ischemic events on clopidogrel were associated with LoF variants (OR 2.2, 95% CI 0.3-14.4) and several cardiovascular risk factors. Associations were not statistically significant in our small study, but plausible and in line with estimates from large prospective studies.

## Conclusion

PGx-guided clopidogrel therapy can identify patients with an elevated risk of ischemic events and offer evidence-based alternative treatments. Successful implementation in clinical practice requires a personalized interdisciplinary service that evaluates indications and additional risk factors, provides specific recommendations and proactively follows their implementation.

## Cohort Study

| CYP2C19 Phenotype | Total n (%) | Change! n | Accepted n |
|---|---|---|---|
| All patients | 56 (100 %) | na | na |
| Normal Metab. | 34 (61 %) | 0 | 0 |
| Rapid Metab. | 4 (7 %) | 0 | 0 |
| Intem. Metab. | 17 (30 %) | 16 | 11 |
| Poor Metab. | 1 (2 %) | 1 | 1 |

## Case-control Study

| Univariate analysis | OR* (95 % CI) |
|---|---|
| CYP2C19 IM or PM | 1.9 (0.4 - 8.7) |
| **Multivariate analysis** | **OR* (95 % CI)** |
| CYP2C19 IM or PM | 2.2 (0.3 - 14.4) |
| Age | 09. (0.1 - 1.0) |
| Female gender | 0.5 (0.05 - 5.87) |
| Diabetes | 3.3 (0.4 - 25.2) |
| Peripheral artery disease | 3.6 (0.4 - 34.1) |
| Cerebrovascular disease | 1.3 (0.2 - 9.5) |
| Dual platelet inhibition (ASS & clopidogrel) | 0.6 (0.1 - 4.6) |

*Odds ratio for recurrent thrombotic event under clopidogrel therapy from univariate analysis and multivariate logistic regression analysis; in the multivariate analysis age is modeled as a continuous variable, all other variables are binary
IM = intermediate metabolizer
PM = poor metabolizer

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