Clopidogrel versus Prasugrel in dual Platelet inhibition on elderly patients with acute coronary syndrome – the CLOPRA study

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This article is dedicated to the memory of LindaTennant

Abstract

Our study carried out in elderly and multimorbid patients with acute coronary syndrome initially treated with ASS (100 mg per day) plus Clopidogrel (75 mg per day) was focused at Clopidogrel low- and non-responders. Moreover, we intended to clarify how far patients with reduced Clopidogrel response can profit by switching to Prasugrel.

In 178 patients (mean age: 74.1 ± 0.6 years) Thrombocyte Reactivity Indices (TRI) were measured by VASP-tests. Patients showing a limited Clopidogrel response (low- and non-responders) were switched to Prasugrel (60 mg loading dose followed by 5 or 10 mg maintenance dose per day; 10 mg as standard dose, 5 mg in patients aged 75 years or older or weighting 60 Kg or less). Patients who were switched to Prasugrel were controlled by further VASP-tests. Additional evaluations were made for several subgroups of different age and gender. All patients were treated in a rehabilitation unit (Clinic "Meduna", Bad Bertrich, Germany), VASP-tests were carried out in a specialized laboratory (Center for Laboratory Diagnostics, Koblenz, Germany).

In elderly patients the fraction of Clopidogrel low- and non-responders tended to higher proportions than in younger patients (34.8 versus 46.8 %). In all cases with limited Clopidogrel response thrombocyte reactivity could be lowered by switching to Prasugrel. In patients of 75 years or older, or weighting less than 60 KG, a daily dose of 5 mg Prasugrel led to the same sufficient reduction of thrombocyte reactivity as in the other patients given 10 mg per day. After drug-switching circa 6 % remained low- or non responders regardless of whether they were treated with 5 or 10 mg Prasugrel. In patients successfully switched to Prasugrel we found the same reduction of thrombocyte reactivity as in Clopidogrel responders (mean TRI: 19%); all of our patients treated as described were free from any bleeding complications.

All in all, Prasugrel seems to be more effective in lowering thrombocyte reactivity also in elderly patients, because the proportion of patients with limited response is much lower than in patients treated with Clopidogrel.

Keywords

1. Introduction

According to generally accepted standards patients with a recent occurrence of acute coronary syndrome (ACS) should have a dual antiplatelet therapy (DAPT) based on ASS plus $P2Y_{12}$ receptor antagonist continued for 12 months; following this, a single thrombocyte aggregation inhibitor - preferably acetylsalicylic acid (ASS) - should be maintained.

Limitations of a dual platelet inhibition with ASS plus Clopidogrel arise from a possible resistance to Clopidogrel, which may be found in 4 to over 30 percent (depending on the author) of all patients treated (**1, 15, 17, 24, 28**). On average, about every third patient shows resistance to Clopidogrel, about every fifth patient to ASS (**19**). Resistance to ASS seems to have similar pejorative effects on the prognosis of subsequent cardiovascular incidents (**29**), as resistance to $P2Y_{12}$ receptor antagonists (**21**). In particular, the risks of subsequent recurrence of ACS and stent-thrombosis are increased (**19, 14, 20**).

Patients proved to be Clopidogrel-resistant can be treated with newer $P2Y_{12}$-receptor-antagonists. Prasugrel is the first representative of this new generation of drugs. It is activated via only one stage of metabolism (**31**), it reaches its level of efficiency faster and induces a stronger maximal platelet inhibition (**31**). Genetic polymorphs of the Cytochrome iso-enzymes have less inhibitory effect on the activation of Prasugrel than in the case of Clopidogrel (**30**). Consequently, variations in efficiency from patient to patient are markedly less obvious than for Clopidogrel (**9**).

According to manufacturers´ recom-mendations (published in Europe), elderly patients ($\geq$ 75 year old) and patients of low weight (< 60 kg) should be given a half

maintenance dose when treated with Prasugrel (5 mg instead of 10 mg). However, this reduction of dose is not generally accepted (and therefore not worldwide recommended up till now). As shown in the GENERATIONS trial, 5 mg Prasugrel lead to adequate platelet inhibition in 155 elderly patients with stabile angina pectoris (**12**).

In our study, 178 elderly patients with ACS are evaluated with regard to their Clopidogrel and Prasugrel response. Based on VASP tests, the efficiency of platelet inhibition achieved with Clopidogrel was compared with that achievable by switching to Prasugrel (5 or 10 mg) in those patients showing a limited Clopidogrel response. It was further evaluated, which responder rates can be achieved when such patients affected with a limited Clopidogrel response are switched to Prasugrel. Lastly, we examined whether differences of age, gender or influences of co-medications or co-morbidity can be proved to affect Clopidogrel resistance. The aggregation inhibitory effect achieved with Prasugrel or Clopidogrel was evaluated in all of our patients and in several patient subgroups; all parameters measured were submitted to comparative statistical analyses.

2. Material and methods

2.1. Patient groups

Inclusion criteria: acute ACS (**N**on **ST E**levation **M**yocardial **I**nfarction/NSTEMI or **ST E**levation **M**yocardial **I**nfarction/ STEMI) treated with ASS (100 mg per day) plus Clopidogrel (75 mg per day).

A total of 178 in-patients was recruited, who were treated in the clinic "Meduna", Bad Bertrich, Germany over a period of two years following a recent acute coronary syndrome (ACS, NSTEMI or

STEMI). Each patient had been previously treated for a few days in an outside acute-care hospital; the acute coronary syndrome had occurred at an average of 7-10 days before admittance here.

Exclusion criteria: Clopidogrel mono-therapy (where ASS was not tolerated), simultaneous treatment with Coumarins and other newer oral anticoagulants (triple-therapy), contra-indications for treatment with Prasugrel according to the generally accepted recommendations (pathologic bleeding, e.g. peptic ulcer, intracranial hemorrhage, prior transient ischemic attack (TIA) or stroke, hypersensitivity).

Each patient accepted for the study was being treated on admission to our clinic with a dual platelet inhibition based on ASS and Clopidogrel and had been provided with one or more coronary stents in the previous clinic (**B**are **M**etal

Stents/BMS or **D**rug **E**luting **S**tents/DES). The majority of the patients belonged to an advanced age group, which showed corresponding multimorbidity and complex accompanying medication. The average age of the total patient group was 74.1 ± 0.6 years (median: 75 years). The average age of all men was 73.0 ± 0.9 years (median: 74 years), that of the women 75.5 ± 0.8 (median: 74 years); the global age structure of the study group is shown in **Fig. 1.** The fractions of men and women were balanced in the total group and in all subgroups analyzed.

Consequent to the advanced age of most patients several additional diseases to be treated were present, requiring a variety of co-medications. The most relevant co-diseases documented are presented in **Tab. 1**, the most relevant medications applied, in **Tab. 2**.
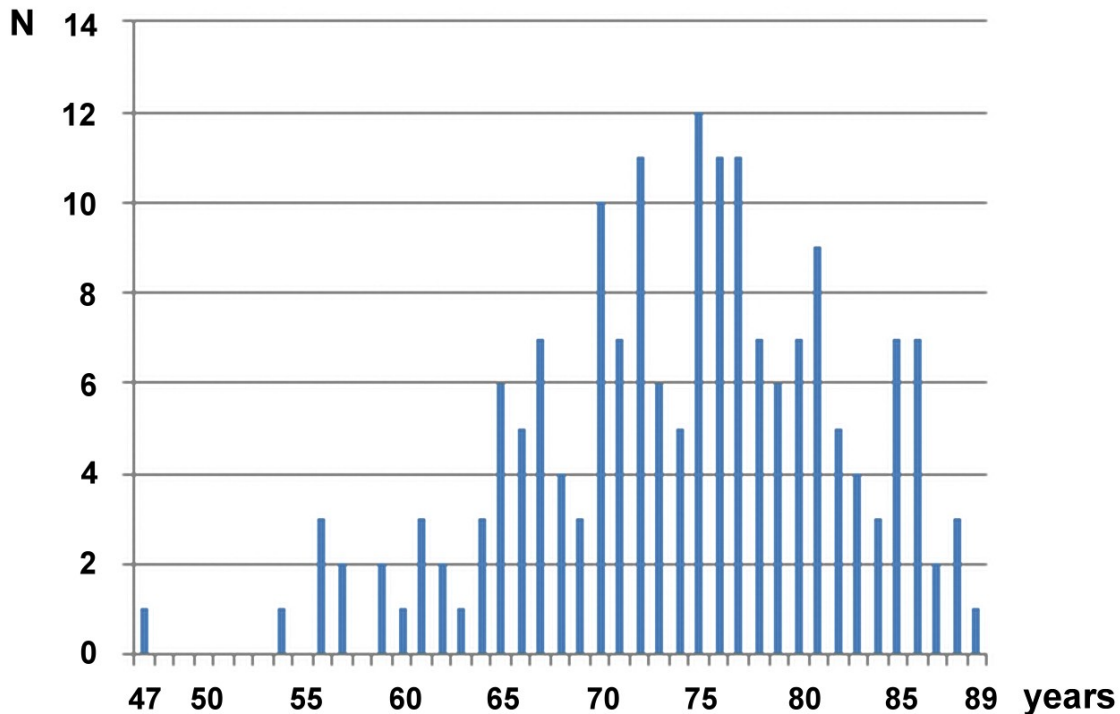

Fig. 1: *Age distribution of all patients examined (N = 178)*

Tab. 1: Cardiac diagnoses and mostly found co-diagnoses (number of patients: ≥ 10) in all patients examined (N = 178)

Diagnosis	Number of patients	Proportion (percent)
NSTEMI	108	61 %
STEMI	70	39 %
3-vessel-CHD	92	52 %
2-vessel-CHD	45	25 %
1-vessel-CHD	41	23 %
DES implantation	95	53 %
BMS implantation	83	47 %
hypertension	140	79 %
dyslipidemia	85	48 %
diabetes mellitus	57	32 %
obesity	39	22 %
renal insufficiency	35	20 %
peripheral arterial occlusion disease	31	17 %
neoplasm	30	17 %
chronic obstructive pulmonary disease	30	17 %
nicotine abusus	21	12 %
depression	20	11 %
hypothyreosis	17	10 %
neurological disorders	16	9 %
hyperuricemia	14	8 %
aortic stenosis	13	7 %
aortic insufficiency	12	7 %
mitral insufficiency	11	6 %
osteoporosis	11	6 %
peripheral artery operation	11	6 %
obstructive sleep apnea	10	6 %
pacemaker	10	6 %

Tab. 2: Most relevant co-medications in Clopidogrel responders and low- or non-responder (number of patients: ≥ 5)

Medications	Number of responders (N = 99)	Fraction of responders (percent)	Number of low- and non resp. (N = 79)	Fraction of low- and non resp. (percent)
duale antiplatelet therapy	99	100 %	79	100 %
lipid-lowering drugs	86	86 %	73	94 %
beta blockers	**79 (!)**	**79 % (!)**	**74 (!)**	**95 % (!)**
diuretics	66	66 %	56	72 %
proton pump inhibitors	65	65 %	50	64 %
ACE inhibitors	60	60 %	51	65 %
calcium channel blockers	19	19 %	21	27 %
angiotensin II rezeptor blockers	21	21 %	17	22 %
L-Thyroxine	14	14 %	17	22 %
Insulin	16	16 %	11	14 %
allopurinol	15	15 %	10	13 %
bronchodilators	15	15 %	8	10 %
antidepressive drugs	10	10 %	10	13 %
dipeptidyl peptidase-4 inhibitors	12	12 %	8	10 %
metformin	14	14 %	1	1 %
nitrates and nitrites	9	9 %	4	5 %
morphine derivates	9	9 %	3	4 %
non steroidal antirheumatic drugs	12	12 %	0	0 %
benzodiazepines	10	10 %	1	1 %
Amiodarone	7	7 %	2	3 %
cortikosteroids	6	6 %	2	3 %
moxonidin	3	3 %	5	6 %
dipyramidole and other cor. dilatators	7	7 %	0	0 %
Tamsulosin	5	5 %	2	3 %
molsidomin	5	5 %	0	0 %
ivabradin	0	0 %	5	6 %

2.2 Laboratory diagnostics

2.2.1. Considerations on methods for measurement of platelet activity

At present, several different procedures are available to carry out in-vitro measurements of pharmacologically induced inhibition of thrombocyte aggregation. These have been described in review articles (**18, 23**). Breet et al. carried out comparative parallel measurements of thrombocyte aggregation using five different test procedures in 1069 coronary patients, who had elective stent implantations: conventional aggregometry, Verify Now, Plateletworks, IMPACT-R and PFA-100. The post-interventional follow-up lasted 12 months. Aggregometry, Verify Now and Plateletworks showed a good correlation with clinical end-points (death, acute coronary syndrome, stent thrombosis, ischemic cerebral insults and hemorrhagic complication), whereas IMPACT-R and PFA-100 showed no significant correlation (**11**).

Paniccia et al. could show, in 1267 patients with acute coronary syndrome, that there are significant correlations and agreements between aggregometry, verify Now and VASP-test (**25**). Especially the VASP-test showed a good correlation to stent-thromboses (**25, 16, 7**). A strong agreement between aggregation measurements with Verify Now and VASP-test could also be shown by Bidget et al. (**5**). VASP-test and Verify Now also showed the best correlation with the plasma concentration of active Clopidogrel metabolites, so that these two tests were particularly recommended for monitoring Clopidogrel-induced platelet inhibition (**10**). The VASP test has a very high prognostic value for ischemic events in patients undergoing treatment with $P2Y_{12}$-receptor antagonists following PCI (**26**).

In contrast to Verify Now, no fresh blood is necessary for a VASP text. Instead, 10 ml of blood can be drawn into standard citrate tubes, as are also used for routine diagnostics in clotting mechanisms. The specimens drawn can be stored at room temperature and can be processed within a time window of 48 hours.

In consideration of all aspects mentioned, we decided to use VASP test for evaluation of Clopidogrel and Prasugrel response.

2.2.2. Diagnostic workflow

VASP tests were carried out by the Center for Laboratory Diagnostics, Koblenz, Germany, based on the method described by Schwarz (**27**). We used a standardized kit from the manufacturer Biocytex (PLT VASP/ $P2Y_{12}$-test); this assay can be used in citrated full blood. Platelets were marked with an antibody coupled with FITC; analyses were made with a flow cytometer Canto II from Becton & Dickinson, Heidelberg, Germany. From each specimen five single analyses were carried out and averaged; variation coefficients were documented for quality control.

In a first phase of our experiment, the VASP-test used was calibrated for several months, using specimens from healthy subjects not under treatment with thrombocyte aggregation inhibitors. These measurements showed a good correlation to reference values given by the manufacturer; in healthy young people the standard value of Thrombocyte Reactivity Index (TRI) was 100%; in healthy elderly persons it could physiologically decrease to circa 70%.

In a second phase of test evaluation, repetitive TRI measurements were carried out in patients under Clopidogrel over a period of three following days.

The "cut-off" value of TRI, which indicates an insufficient aggregation inhibition, and thus a lack in response to the respective platelet inhibitor, was defined by Bonello as $\geq 50\%$ (**8, 6**). Thus, an index of $\geq 50\%$ shows by definition a non-responder.

Through our comparative measurements in identical patients we could, however, show that the VASP test is affected with a relevant variation of values measured -, in a range which is comparable with usual enzymatic tests in laboratory medicine. Thus, for instance, repeated measurements in the same person, beginning with a reactive index of 50%, could "spontaneously" be reduced by 10, corresponding to a value of 40%. Consequently we determined that TRI between 40% and 50% corresponds to a diagnostic "shady or grey area" or to a questionable responder status, and so we defined patients with measurements in this area as "low responders". Sufficient

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platelet inhibition under Clopidogrel (status of a definite responder) we thus categorized as a TRI ≤ 40%.

Following these evaluation phases we started with routine measurements in elderly ACS patients treated with $P2Y_{12}$ inhibitors over a period of two following years.

All patients in the study group were tested for thrombocyte- reactivity within the frame work of the routine lab-work on the day of admission. For this purpose, 10 ml of citrate blood (the usual "clotting monovette") were processed on the same day by a specialized laboratory. All specimens were taken in the morning between 7.00 and 9.00, the laboratory analyses were performed in the afternoon of the same day.

2.2.3. Clinical and therapeutic workflow

All patients with a recent ACS, who fulfilled the inclusion criteria, underwent a VASP-test on the day of admission to determine their responder status under the initially existent dual platelet inhibition with ASS plus Clopidogrel. Those patients with a TRI under 40% were accepted as definite Clopidogrel responders, so that the dual platelet inhibition was carried on unchanged.
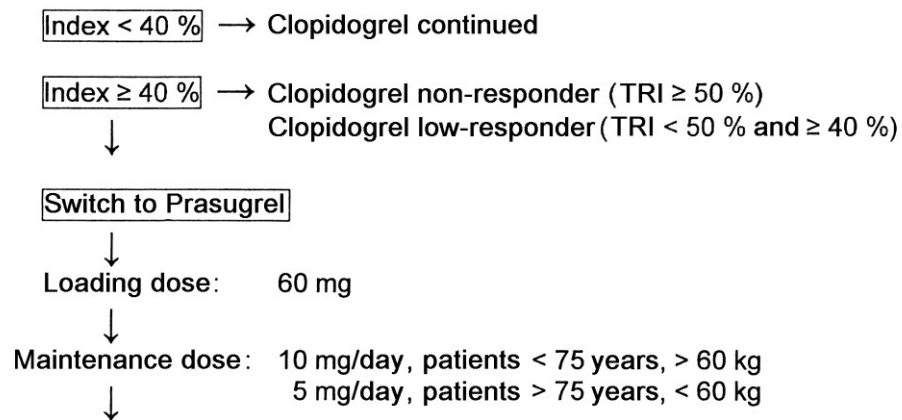
All non-responders (reactivity index ≥ 50%) and also all low-responders (TRI 40% or more, but less than 50%) were changed to Prasugrel directly on receiving the test results. This switching was carried out as an individual therapeutic decision of the physician responsible for the patients care, based on the patient´s information and agreement. As only those patients were switched to Prasugrel who showed a limited Clopidogrel response and agreed with this modification of their medication based on an intensive personal conversation and individual medical advice, ethical approval was not necessary according to the given German law. On the first day, a loading dose of 60 mg Prasugrel was given, from the second day on, the specific maintenance dose. Patients under 75 years weighting more than 60 kg were given a daily maintenance dose of 10 mg, patients of 75 years or older, or weighting less than 60 kg were given a daily dose of 5 mg Prasugrel.

8-10 days after change of therapy a VASP-test was carried out as a check on low- and non-responders switched to Prasugrel. In this way it could be determined how many Clopidogrel low- or non-responders con-verted to responders through change to Prasugrel. In the subgroup of patients on 5 mg Prasugrel it could also be tested how effective this daily-half dose was as a practical alternative with regard to responder status. Those few patients who did not show an appropriate reactivity index in the therapeutic spectrum under 5 mg Prasugrel were dismissed with a recommendation to increase the daily dose to 10 mg and later carry out a further control of the reactivity index on an out-patient basis

The flow diagram in **Fig. 2** gives an overview of the design and "work flow" of our study.

Initial thrombocyte-reactivity (VASP-test)

Index < 40 % → Clopidogrel continued

Index ≥ 40 % → Clopidogrel non-responder (TRI ≥ 50 %)
↓   Clopidogrel low-responder (TRI < 50 % and ≥ 40 %)

Switch to Prasugrel
↓
Loading dose: 60 mg
↓
Maintenance dose: 10 mg/day, patients < 75 years, > 60 kg
↓   5 mg/day, patients > 75 years, < 60 kg

Thrombocyte-reactivity in patients switched to Prasugrel

Index < 40 % → Prasugrel continued
↓

Index ≥ 40 % → Prasugrel non- or low-responder
↓
Adjustment of Prasugrel dose
or switch to other drugs
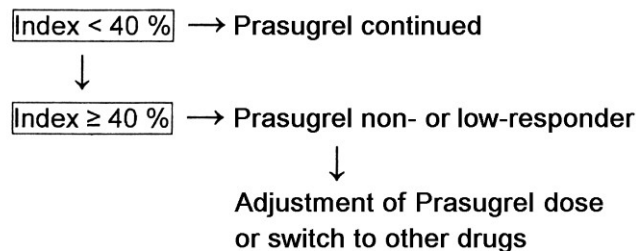
Fig. 2: "Work flow" of TRI measurements and drug switching

2.2.4. Statistical tests

Qualitative characteristics of the total group and of some sub-groups were tested for statistical significance using the Chi-Square-test. For quantitative statistic analyses (testing the significance of various quantitative deviations) IBM® SPSS® Statistics Version 22 (recent upgrade for 2013) for MAC was used. The normal scatter was tested by the Kolmogorov-Smirnov-test. Differences between groups were analyzed using the T-test and Mann-Whitney-U-test.

3. Results

3.1. Basic results

The fractions of low- and non responders in the total group and four patient sub-groups (75 years and above, 70 years and above, 70 up till 75 years, and 69 years or younger) are shown in **Fig. 3**. It is clearly to see that the problem of Clopidogrel resistance remains highly relevant in patients of advanced age, independent of gender.
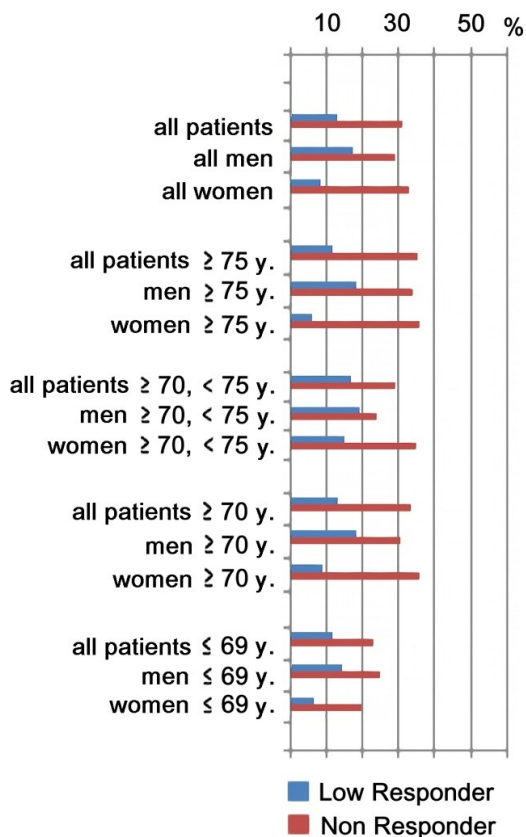
Fig. 3: Fractions of Clopidogrel low- and non-responders in several sub-groups of patients examined [%]

Of the total of 79 patients who were detected as non responders (N = 57) or low responders (N = 22), 46 patients (58 % of those affected) could be switched from Clopidogrel to Prasugrel during their stay in our clinic. In the sub-group of patients aged over 75 (N = 94) containing 33 non-responders and 11 low-responders, 25 patients (56 %) could be switched to Prasugrel. The larger sub-group of patients

aged 70 years and more contained 63 low- and non-responders (45 non-responders and 18 low-responders); of these, 36 patients (57 %) could be switched to Prasugrel.

The remaining low- and non-responders were not switched to Prasugrel, either because the patients themselves refused or they were dismissed from inpatient-care before completion. Nevertheless, all of these low- and non-responders who were not switched over by us were recommended to change to Prasugrel.

All in all, we did not see any complications associated with DAPT either in patients treated with Clopidogrel or in those patients who were switched to Prasugrel, in particular, we did not see any bleeding.

3.2. Change in the responder status after switching from Clopidogrel to Prasugrel

In the total of 46 patients who were switched from Clopidogrel to Prasugrel, a repeat check of the VASP-test was carried out 8-10 days after switching. From the measurements gained in this way, we could quantitatively derive all reductions of original TRI values achieved by switch to Prasugrel calculated in percent for all of these patients and subgroups mentioned above (see section 3.1). The results of these calculations are shown in **Fig. 4.**
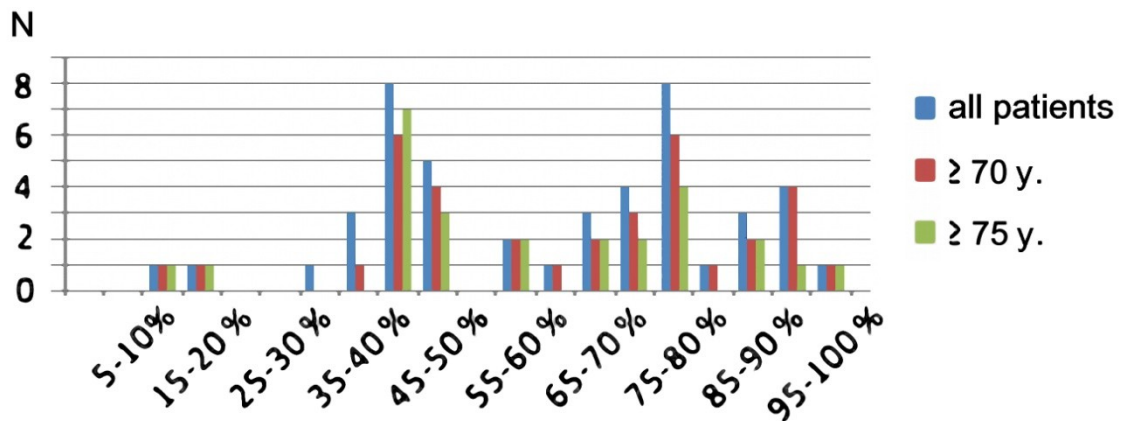
Fig. 4: *Reductions of TRI achievable by drug switching from Clopidogrel to Prasugrel, evaluated in Clopidogrel low- and non-responders, calculated in percent and demonstrated for several categories of age range*

In the total group the initial values of TRI determined in all low- and non-responders could be decreased by 57% on average (arithmetic mean) or by 63% (median). A similar reduction was also shown in the sub-group of patients of 70 years or above (reduction by 58 or 63 %, arithmetic mean and median). In the sub-group of patients aged 75 years or more, there resulted an average reduction of the originally measured reactivity indices by 53-54 % (median or arithmetic average). On the whole, no patient was noted where the switch from Clopidogrel to Prasugrel had not caused a reduction in the reactivity indices originally measured. Thus, the entire low- and non-responders could reduce their initially measured values by switching to Prasugrel.

In spite of this favorable effect, a total of six patients was noted who could not be brought into a responder status, as defined, by changing to Prasugrel. These cases are sketched briefly in **Tab. 3**.

Tab. 3: Prasugrel low- and non-responders (N = 6)

Age (years)	Gender	TRI I (%)	TRI II (%)	Dose of Prasugrel (mg)
77	fem.	60	56	5
76	fem.	71	42	5
73	fem.	80	56	5
67	male	67	50	10
56	male	75	50	10
56	male	71	50	10

3.3. Quantitative statistical analyses of the Thrombocyte Reactivity Indices (TRI) measured

An overview of all TRI measurements carried out is given in **Fig. 5**. Obviously, patients showing a limited Clopidogrel response could be successfully converted to adequate platelet inhibition by switching to Prasugrel (p ≤ 0.0001). Significant age- and gender-dependent differences could not be proved.

For the subgroup of 46 Clopidogrel low- and non-responders, who could be switched to Prasugrel during the rehabilitation treatment, the relevant, originally measured TRI under Clopidogrel was 59.39 ± 1.72 %, SD: 11.7 %, median: 58%, range: 40-83 %. If the six patients previously mentioned, who did not achieve the so-defined responder status even after switching medication, were removed from the group, 40 definite Prasugrel responders remain. These showed under Prasugrel an average TRI of 20.6 ± 1.50 %, SD: 9.5 %, median: 19 %, range: 7-36. This corresponds to the average TRI under Clopidogrel response (19.08 ± 1.16 %).

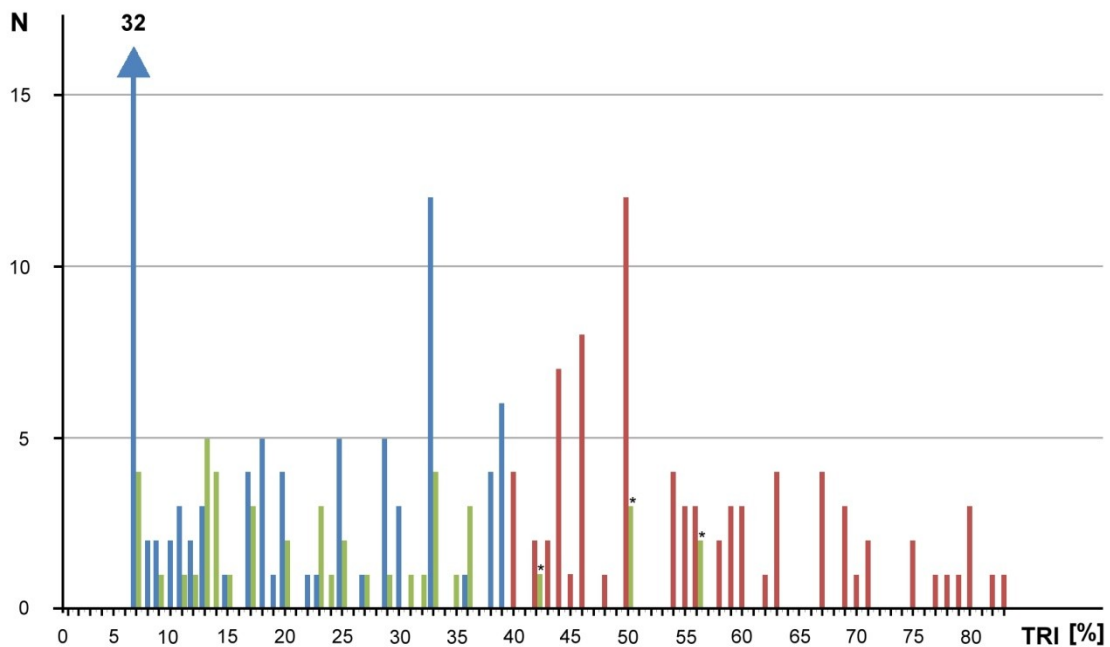***Fig. 5:*** *Overview of all TRI values measured.*
Blue: Clopidogrl responders (N = 99, mean TRI: 19.8 ± 1.16 %, SD:11.5 %, median: 17 %, range: 7-39 %). Red: Clopidogrel low- and non responders (N = 79, mean TRI: 56.52 ± 1.36 %, SD: 12.1 %, median: 54 %, range: 40-83 %). Green: Patients switched to Prasugrel (N = 46, mean TRI: 24.52 ± 2.01 %, SD: 13.6 %, median: 23 %, range: 7-56 %). * = Prasugrel low- and non-responders

In the 46 patients switched to Prasugrel an additional sub-group comparison with regard to age was carried out, in order to compare the therapeutic effects of a dose of 10 mg Prasugrel (standard dose up till 74 years) as opposed to the reduced standard dose of 5 mg at ages of 75 years and older.

In the Clopidogrel low- and non-responders who were younger than 75 years (N = 21), the average TRI original

value under Clopidogrel was 58.33 ± 2.51 % (median: 58%, range: 45-82 %). In the corresponding patients who were 75 years or older (N = 25), there was an original value of 60.28 ± 2.39 % (median: 56 %, range: 40-83 %). These tiny differences in the measured values of both sub-groups were statistically not significant. After changing to Prasugrel (10 mg before 74 years, 5 mg over 75 years) the TRI was highly significantly reduced in both age groups ($p \leq 0.0001$). In the under 75-year-olds, there was a TRI value of 23.38 ± 3.43 % (median: 17%, range: 7-56%). In those patients aged at least 75 years, the corresponding TRI was 25.48 ± 2.37% (median: 25 %, range: 7-56 %): The tiny numerical difference in TRI values of younger and older patients (23.38 versus 25.48 %) was statistically not significant. Thus, it may be deduced that at an age over 75 years, a daily dose of 5 mg Prasugrel can achieve the same measurable effect as a 10 mg dose in a younger patient.

3.4. Evaluation of Co-morbidity

Clopidogrel low- and non responders were not affected with simultaneous diseases in significantly higher proportions when compared with responders. Thus, none of the various co-diseases being immanent in the study group was associated with a higher proportion of non responders.

4. Discussion

According to our findings, up to 50 % of elderly patients who survived ACS are affected with a limited Clopidogrel response whereas only 6 % of patients switched to Prasugrel remain in a low- or non-responder status. The rate of Clopidogrel low- and non-responders does not decrease with increased age, but rather potentially increases. Men also seem to be more commonly affected, on the whole, by Clopidogrel resistance, than women. These

trends, however, cannot be statistically confirmed as significant in the patient groups examined. Nevertheless, it can be derived from these findings that elderly patients suffering from ACS may have a significant benefit when treated with ASS plus new generation P2Y12 receptor antagonists instead of Clopidogrel so that they should be preferably treated by such a newer DAPT regime. In the future clinical outcome studies should be planned in order to confirm this plausible hypothesis.

As an essential result of the data collection presented, it can be noted that in all patients examined who had a decreased Clopidogrel response, a reduction in the thrombocyte reactivity index can be achieved by switching to Prasugrel - even in patients of advanced age beyond 70 or 75 years. This result corresponds with other findings evaluated on patients who were electively treated with coronary stents without running through a previous acute coronary syndrome (**4**). The vast majority of "switched" patients can also per definitionem be moved from the low- or non-responder status to a responder status; only in a few individual cases no so-defined response can be achieved by drug switching (3 % low- and 3 % non - responders). This finding corresponds with results of the ACAPULCO study (**32**); in this study, carried out with younger patients, up to 6 % non-responders were found under Prasugrel and up to 34 % under Clopidogrel.

It can also be deduced from our study that in the vast majority of aged patients with ACS, an effective response can be achieved using the reduced dose of 5 mg Prasugrel daily. The TRI values of the elderly rehabilitation patients treated with 5 mg correspond to those of the younger patients treated with 10 mg Prasugrel. This finding confirms corresponding results evaluated in 155 patients with stable coronary artery disease (GENERATIONS

trial, **12**). Moreover, Clopidogrel low- and non-responders can achieve aggregation inhibition of comparable standard to Clopidogrel responders through switching to Prasugrel.

Clopidogrel-drug interactions have been described by several authors (**2, 3, 13, 22**). In our study group we compiled all co-medications (see Table 2), but the design of our trial was not intended to establish such interaction. We recommend making further separate studies to evaluate drug interactions with sample specifically selected for that aim.

Although our patients were affected with several co-diseases, none of these diseases was associated with limited Clopidogrel response in a higher proportion when compared with responders. This finding can also be regarded as unexpected, too, because especially renal insufficiency and diabetes mellitus can modulate therapeutic effects of drugs and drug interactions in many cases.

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