



Original article

 Aspirin non-responsiveness as measured by PFA-100 in patients with
coronary artery disease

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Abstract

Introduction: The purpose of the present study was to study the concept of aspirin resistance or non-responsiveness by investigating the response to long-term aspirin therapy in patients with a former acute myocardial infarction (AMI). **Materials and methods:** Patients with an AMI ($n=202$) randomly assigned to aspirin 160 mg/day ($n=71$), aspirin 75 mg/day and warfarin (INR 2.0–2.5) ($n=58$) or warfarin (INR 2.8–4.2) ($n=73$) were evaluated by the PFA-100[®], biochemical variables and clinical events after a mean treatment period of 4 years. **Results:** The limit for being an aspirin non-responder was defined as the 95th percentile value in the warfarin alone group (196 s) with the epinephrine cartridge. In patients on aspirin alone 25/71 (35%) were non-responders and on the combination 23/58 (40%). With the adenosine diphosphate (ADP) cartridge only minor differences were found. The levels of thromboxane B₂ in both aspirin groups, in responders as well as in non-responders, were extremely low compared to the warfarin alone group. Evaluating both aspirin groups together ($n=129$), the levels of soluble P-selectin were significantly higher in non-responders as compared to responders ($p=0.012$). During the observation period of 4 years with limited number of events, there was a tendency for higher event rates in non-responders as compared to responders (36% vs. 24%, $p=0.28$). **Conclusions:** In our evaluation of the PFA-100[®] a considerable number of post-AMI patients seemed to be non-responders to long-term aspirin therapy in doses of 75 and 160 mg/day. Circulating levels of P-selectin were higher in the non-responders. A tendency to higher incidence of clinical events among non-responders was observed.

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Keywords: Antiplatelet therapy; Aspirin resistance; Aspirin non-response; P-selectin; PFA-100; Secondary prophylaxis

1. Introduction

Aspirin is commonly used for primary and secondary prevention against thromboembolic complications of atherosclerotic disease, and its effects are well documented [1].

However, some patients on aspirin treatment still experience thromboembolic events, and the possible individual variation in the response to aspirin has been discussed. Several studies have, by using different methods of measuring platelet activity, shown individual variations in the

influence of aspirin treatment [2–7]. This has led to the introduction of the concept of aspirin resistance or non-responsiveness.

Laboratory methods for evaluation of platelet function are complicated and time-consuming. Levels of beta-thromboglobulin (β -TG) and soluble P-selectin have in some studies been used as markers of platelet activation [8,9], whereas platelet response to aspirin treatment has mostly been evaluated by platelet reactivity (PR) index [3], platelet aggregate ratio (PAR) [7], conventional platelet aggregation [4–6] and cutaneous bleeding time [2]. The inconsistency of the results related to aspirin response with the different methods used have contributed to confusion in this field. As most studies document a substantial inhibition of the production of thromboxane A₂ in all patients studied, the term aspirin resistance seems inappropriate.

The clinical relevance of this possible lack of response to aspirin treatment has been investigated by Grottemeyer et al. [10]. With the PR test used they showed, in stroke patients treated with aspirin 500 mg three times daily for 2 years,

Abbreviations: ADP, adenosine diphosphate; AMI, acute myocardial infarction; β -TG, beta-thromboglobulin; CABG, coronary artery bypass graft; CT, closure time; EPI, epinephrine; INR, international normalized ratio; mg/day, milligrams per day; PCI, percutaneous coronary intervention; s, seconds; WARIS II, Warfarin–Aspirin Reinfarction Study.

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that 5 out of 114 (4.4%) responders and 24 out of 60 (40%) non-responders suffered an endpoint defined as stroke, myocardial infarction or vascular death.

In the study of Buchanan et al. [11] in patients undergoing coronary artery bypass grafting (CABG) treated with 325 mg aspirin daily, cutaneous bleeding time was used to identify non-responders. They could not demonstrate any statistically significant differences between responders and non-responders in thrombotic events after 2 years of follow-up.

With the recent introduction of the PFA-100[®] method, studies of platelet function especially related to the influence of aspirin have become more convenient and suitable for clinical practise. PFA-100[®] is a simple and rapid method to determine platelet function where whole blood samples can be kept at room temperature for up to 4 h after sample collection before analysis.

The purpose of the present study was to investigate the response to long-term aspirin therapy in a population of patients with a former acute myocardial infarction (AMI), evaluated by the PFA-100[®]. In addition, we wanted to study the reproducibility of the test over several months. The relation between the tested response to aspirin and clinical events during 4 years of follow-up was also recorded.

2. Materials and methods

A subset of patients included in the Warfarin–Aspirin Reinfarction Study (WARIS) II trial [12] was studied. Two hundred and two patients with AMI had been randomly assigned to treatment with aspirin (Albyl-E, Nycomed Pharma, Norway) 160 mg/day ($n=71$), aspirin 75 mg/day and warfarin (Marevan, Nycomed Pharma) with target INR 2.0–2.5 ($n=58$) or warfarin alone with target INR 2.8–4.2 ($n=73$).

After a mean treatment period of 4 years, platelet function was evaluated by the PFA-100[®] (Platelet Function Analyzer, Dade Behring, Leiderbach, Germany) in a fasting state 24 h after the last dose of aspirin. Citrated blood (0.129 M trisodium citrate in dilution 1:10) was used and the analyses were performed within a range of 30 min and 2 h after blood collection. The PFA-100[®] evaluates platelet function by determining the time to occlusion of an aperture in a membrane coated with collagen and adenosine diphosphate (ADP) or epinephrine (EPI) as citrated whole blood flows under high shear stress conditions.

Measurements of time to aperture occlusion (closure time, CT) were performed using both a collagen/EPI cartridge and a collagen/ADP cartridge. After 300 s, the process automatically terminates, inferring that longer CT's will be reported as 300 s. According to the manufacturer, in healthy individuals, CT ranges with EPI are reported to be 94–193 s, and 71–118 s with ADP. The inter-assay coefficient of variation (CV%) in our laboratory was <4% for both (different individuals with 10 parallel samples from

each were analysed on the same day). The same batches of the PFA-100[®] cartridges were used throughout.

In addition, the following measurements were made: platelet count and volume determined by conventional methods using EDTA blood and performed within 4 h; β -TG determinations in CTAD-plasma (containing sodium citrate, theophylline, adenosine and dipyridamole), handled according to the manufacturer (Diatube H, Diagnostica Stago, Asnières, France) (Asserachrom β -TG, Diagnostica Stago); soluble P-selectin in citrated plasma separated within 1 h (R&D Systems Europe, Abingdon, Oxon, UK); serum thromboxane B₂ measured with a method previously described [13]. In brief: vacutainer tubes without anticoagulants were kept at 37 °C for 1 h before centrifugation to allow maximal generation of thromboxane A₂.

To study the stability of aspirin response over time, 40 of the patients in the aspirin alone group were re-examined with the PFA-100[®] after a further 4 months, and 20 of these were examined a third time after an additional 4 weeks.

In the WARIS II trial, the main endpoint was combined including death, non-fatal reinfarction and stroke. In the present setting, only non-fatal reinfarction and stroke could be counted in the survivors that were tested. In addition, the secondary endpoint of need for revascularizations (CABG or percutaneous coronary intervention (PCI)) was recorded.

2.1. Statistics

All continuous variables are given as median value and 25,75 percentiles, while categorical variables are given as percentages.

Demographic variables were tested for differences between the treatment groups by one-way analysis of variance (ANOVA).

Assuming skewed distribution, especially of the CT values, nonparametric tests were used. Kruskal–Wallis test

Table 1
Some demographic variables of the patients in the three study groups

	Aspirin (160 mg)	Aspirin (75 mg + warfarin)	Warfarin	<i>p</i>	
<i>n</i>	71	58	73		t1.1
Age (years) ^a	65.8 (43–81)	67.3 (47–81)	66.4 (44–82)	0.910	t1.2
Sex (male %)	79	74	77	0.821	t1.3
Current smoker (%)	35	22	34	0.268	t1.4
Diabetes mellitus (%) ^b	7	10	4	0.381	t1.5
Hypertension (%) ^b	13	24	22	0.205	t1.6

p values refer to differences between treatment groups.

^a Median values (range).

^b At randomization in the WARIS II trial.

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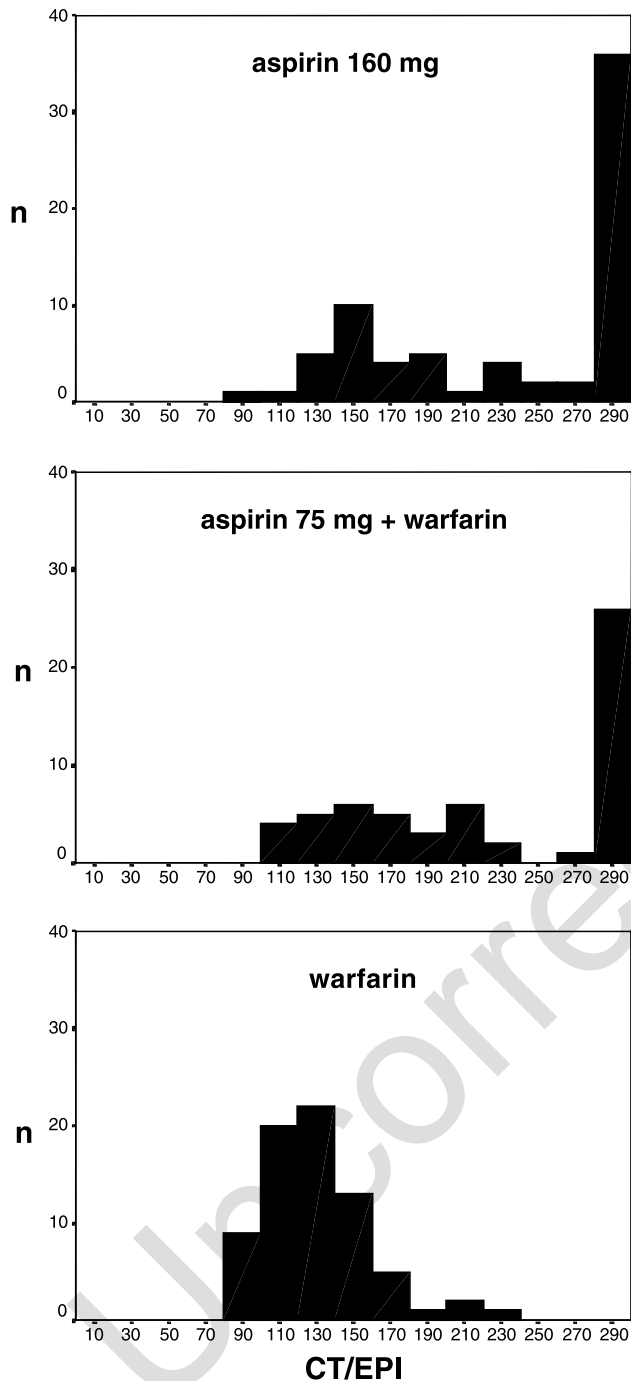


Fig. 1. Distribution of the CT's measured with CT/EPI in the different treatment groups.

147 was used for comparison of all treatment groups, and
 148 Mann–Whitney's rank sum for comparison of individual
 149 group differences, and of the differences between respond-
 150 ers and non-responders. Chi-square test was used to
 151 evaluate the differences in the numbers of responders in
 152 the two aspirin groups, and for differences in the appear-
 153 ance of clinical events in the aspirin alone group. A two-
 154 tailed value of $p < 0.05$ was considered statistically sig-
 155 nificant.

The statistical analyses were performed with SPSS for 156
 Windows version 10.0 package. 157

3. Results 158

Some demographic variables of the patients in the three 159
 study groups are given in Table 1. There were no statisti- 160
 cally significant differences between the groups. 161

The CT's measured with the collagen/epinephrine (CT/ 162
 EPI) are presented in Figs. 1 and 2. Median (25,75 per- 163
 centiles) CT/EPI was 293 s (164,300) on aspirin (160 mg/day) 164
 alone, 227 s (159,300) on the combination of warfarin and 165
 aspirin (75 mg/day) and 123 s (111,145) on warfarin alone. 166
 In patients on aspirin (both groups), the CT/EPI were 167
 significantly higher than in those on warfarin alone 168
 ($p < 0.001$ for both), while there was no statistically sig- 169
 nificant difference between the two aspirin groups. CT/EPI 170
 levels > 300 s were not obtained in any patient on warfarin 171
 alone, in 26/58 (45%) on the combination and in 35/71 172
 (49%) on aspirin alone. 173

We defined the 95th percentile of the CT/EPI in the 174
 patients on warfarin alone as the limit for being aspirin non- 175
 responder (≤ 196 s). On aspirin alone, 25/71 (35%) pre- 176
 sented as non-responders and on the combination, 23/58 177
 (40%) ($p = 0.603$). 178

The CT's with the collagen/ADP cartridge (CT/ADP) 179
 were median 81 s (25,75 percentiles 74,99) on aspirin alone, 180
 76 s (67,98) on the combination and 75 s (67,87) on 181
 warfarin alone. In patients on aspirin alone, the CT/ADP 182
 were significantly higher than in those on warfarin alone 183
 ($p = 0.002$), while there were no statistically significant 184
 differences between the other groups. 185

The levels of thromboxane B_2 are shown in Table 2. As 186
 can be seen, in both aspirin groups, in responders as well as 187

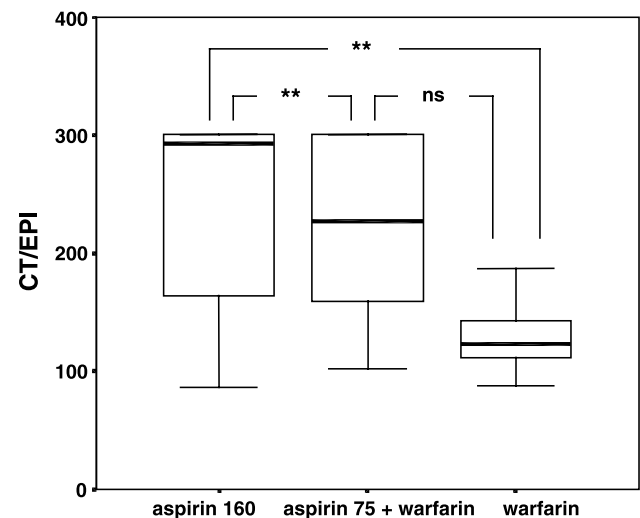


Fig. 2. Median values, 25,75 percentiles and range of the CT's measured with CT/EPI in the different treatment groups. $**p < 0.001$.

t2.1 Table 2

t2.2 Thromboxane B₂, platelet counts, mean platelet volume, β-TG and P-selectin in the three study groups, and according to aspirin responsiveness

t2.3		Aspirin (160 mg)		Aspirin (75 mg + warfarin)		Warfarin	Both aspirin groups	
t2.4		Responders	Non-responders	Responders	Non-responders		Responders	Non-responders
t2.5	<i>n</i>	46	25	35	23	73	81	48
t2.6	Thromboxane B ₂ (ng/ml)	2 (0,2)	2 (1,2)	4 (2,8)	2 (1,10)	198* (185,258)	2 (1,6)	2 (1,4)
t2.7	Platelet count × 10 ⁹ /l	206 (182,231)	224 (201,250)	202 (169,231)	187 (176,217)	201 (168,234)	205 (174,231)	212 (180,241)
t2.8	Mean platelet volume (fl)	10.9 (10.2,11.4)	10.7 (10.4,11.4)	10.5 (10.0,11.2)	10.5 (10.2,11.1)	10.4 (9.9,11.2)	10.7 (10.1,11.2)	10.7 (10.3,11.1)
t2.9	β-TG (IU/ml)	25.3 (19.1,39.7)	30.4 (19.9,41.7)	30 (20.8,43.5)	27.7 (22.9,39.3)	32.9 (20.2,56.2)	27.8 (19.8,40.4)	28.3 (21.8,39.8)
t2.10	P-selectin (ng/ml)	43.3 (35.8,50.0)	48.7 (37.5,55.5)	42.6 (34.0,47.9)	44.8 (40.8,50.5)	42.8 (37.3,52.0)	42.6 (35.0,48.4)	46.4 [†] (39.5,54.1)

t2.11 Values are given as medians (25 and 75 percentiles).

t2.12 **p* < 0.001 for difference from the aspirin groups.

t2.13 [†]*p* = 0.012 for difference from responders.

188 in non-responders, the levels were extremely low compared
 189 to the warfarin alone group (*p* < 0.001 for both), indicating
 190 good compliance of aspirin intake, and inhibition of the
 191 cyclooxygenase pathway.

192 The data on platelet counts, platelet volume, β-TG and
 193 soluble P-selectin are also presented in Table 2. There were
 194 neither statistically significant differences between the treat-
 195 ment groups, nor between aspirin responders and non-
 196 responders within the treatment groups. However, evaluat-
 197 ing both aspirin groups together, the levels of P-selectin
 198 were significantly higher in non-responders as compared to
 199 responders (*p* = 0.012).

200 The individual results (CT/EPI) of the 40 patients (20
 201 responders and 20 non-responders) from the aspirin alone
 202 population who were re-tested 4 months later are visualized
 203 in Fig. 3. Four patients (10%) demonstrated a change that

204 made them cross the line between responder and non-
 205 responder. Among the 20 patients of whom 13 were
 206 responders and 7 non-responders initially, who were tested
 207 a third time after another 4 weeks, two patients (10%) now
 208 crossed the line, one of whom was a responder at the initial
 209 test, non-responder at the second test and responder again at
 210 the last test.

211 During the mean observation period of 4 years, 7
 212 patients in the aspirin alone group suffered a primary
 213 non-fatal event predefined as AMI or thromboembolic
 214 stroke, and 18 were revascularized (Table 3). Among the
 215 non-responders, 3 out of 25 patients (12%) suffered a
 216 primary event, as compared to 4 out of 46 (8.7%) among
 217 the responders. Among the non-responders, 9 (36%) were
 218 revascularized, as compared to 9 (20%) among the res-
 219 ponders. Counting all patients with any clinical event, the

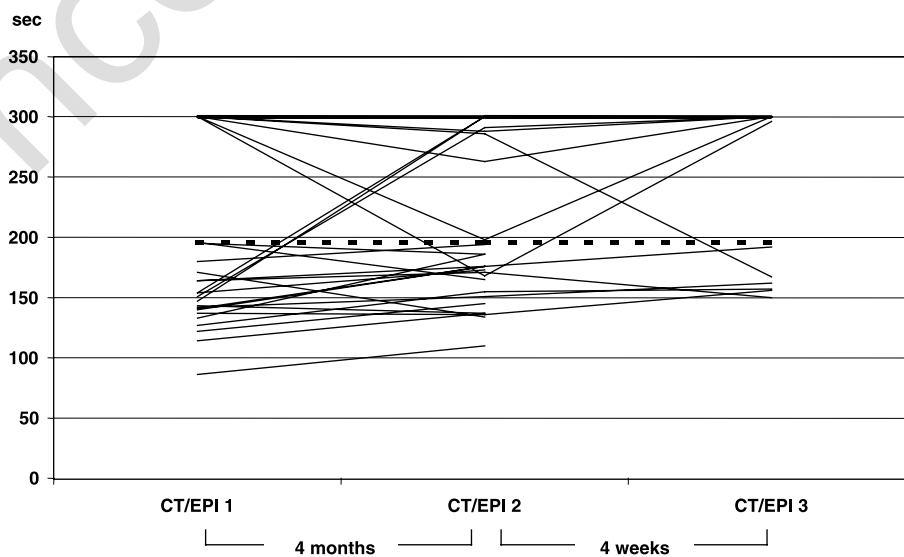


Fig. 3. CT/EPI (s) in patients re-tested. CT/EPI 1 is the initial test (*n* = 40), CT/EPI 2 the test 4 months later (*n* = 40) and CT/EPI 3 the test after another 4 weeks (*n* = 20). The dotted line at CT 196 s represents the cut-off between responders and non-responders. The thicker line at CT 300 s represents all the patients who reached the maximum CT 300 s. The rest of the lines represent one patient each.

t3.1 Table 3

t3.2 Clinical events according to aspirin responsiveness

	Responders		Non-responders		<i>p</i>
	<i>n</i>	(%)	<i>n</i>	(%)	
t3.5 Non-fatal myocardial infarction or thromboembolic stroke	4/46	8.7	3/25	12	0.691
t3.6 Revascularization	9/46	19.6	9/25	36	0.128
t3.7 Any clinical non-fatal event	11/46	23.9	9/25	36	0.280

t3.8 Number of patients suffering a clinical event in the group of patients treated with aspirin alone (*n* = 71), after a mean observation period of 4 years.t3.9 *p* values refer to differences between responders and non-responders.

220 numbers were 9 (36%) among the non-responders and 11
 221 (24%) among the responders. Statistically, no significant
 222 differences were obtained.

223 4. Discussion

224 Our results show that, measured by the PFA-100®
 225 method with the collagen/EPI cartridge 24 h after the last
 226 aspirin intake, a large number of post-AMI patients seems to
 227 be non-responders to aspirin. As also described by others
 228 [2,5–7,14], we found a certain tendency to dose–response,
 229 although not statistically significant. By our definition of
 230 response, there were 40% of non-responders in the group
 231 taking 75 mg aspirin daily, and 35% in the group taking 160
 232 mg aspirin daily. These figures are quite high compared to
 233 some earlier reports.

234 The higher dose of aspirin used in some other studies [3–
 235 6] may, due to the tendency to dose–response, partly
 236 explain the lower prevalence of aspirin non-responders
 237 found in these studies.

238 In the present study, measurements were made 24 h after
 239 the last aspirin intake. Previous studies have indicated an
 240 effect of time, with the larger effect of aspirin 2 h after tablet
 241 intake, and reduced effect after 12 and 24 h [3,7]. This may
 242 also partly explain the higher number of non-responders in
 243 our study compared with others where the tests were
 244 performed more shortly after intake. In some studies, the
 245 time relation between medication and blood sampling was
 246 not reported. Thus, in spite of the long duration of the effect
 247 of aspirin upon platelets, it seems important to standardize
 248 the interval between tablet intake and testing for aspirin
 249 response, even within the first 24 h.

250 One might argue that our cut-off level between respond-
 251 ers and non-responders (196 s defined as the 95th percentile
 252 of the CT obtained in patients with a former myocardial
 253 infarction currently treated with warfarin) is arbitrary, and
 254 that choosing another cut-off level would result in a differ-
 255 ent percentage of non-responders. However, our cut-off
 256 level corresponds with that reported by Mammen et al.
 257 [15] (191 s defined as the 95th percentile in healthy adults)
 258 and is also in accordance with the upper reference limit
 259 described by the manufacturer.

Most other studies have used other methods than the
 PFA-100® to evaluate platelet function, which obviously
 might also influence the numbers of responders/non-res-
 ponders found.

With the ADP cartridge, there were only small differ-
 ences between the treatment groups. Although the differ-
 ence between the aspirin alone and the warfarin alone
 groups was statistically significant, this difference is prob-
 ably too small for any practical use on the individual basis.
 The latter suggestion is in accordance with other findings
 indicating that the ADP cartridge is not sensitive to aspirin
 [14–18].

As also known from the literature [2], and documented in
 the present study, thromboxane B₂ levels are very low in
 patients taking aspirin, independent of so-called aspirin
 responsiveness. The platelets in non-responders as a group
 are obviously not resistant to aspirin, as their cyclooxygenase
 is largely inhibited. The sensitivity to very low levels of
 thromboxane A₂ in an individual is unknown, and with the
 method used one could not disregard that very low amounts
 still are present, thus implying true aspirin resistance. How-
 ever, in these patients as a group their activity and behaviour
 in various tests of platelet function are not influenced as
 expected with aspirin therapy. We have chosen the term
 aspirin non-response to describe this phenomenon. The most
 likely explanation for this phenomenon is that these individ-
 uals mainly activate their platelets via other pathways,
 independent of cyclooxygenase, for instance initiated by
 thrombin. In the present patient population with myocardial
 infarction, this thrombin pathway might be particularly
 relevant, as local thrombin generation is thought to be of
 major importance in atherothrombotic disease states [19].

There were no significant differences in platelet counts or
 platelet volume between the treatment groups, or between
 responders and non-responders. Thus, aspirin treatment and
 response as measured by the PFA-100® did not seem to be
 reflected by the number or volume of the platelets in the
 present study. We also did not find any correlation with the
 levels of β-TG. The levels of P-selectin, on the other hand,
 were significantly higher in the non-responders. This obser-
 vation would fit with the suggestion that non-responders
 have more activated platelets despite aspirin treatment. The
 different expression of β-TG and P-selectin might be dis-
 cussed by their reflection of different mechanisms of platelet
 physiology [8].

Our findings when re-testing the CT/EPI in patients on
 aspirin alone indicate that the measurements are reasonably
 stable over time. Ten percent of the patients tested in each
 interval of time crossed the line between responder and non-
 responder, including one who was a responder at the initial
 test, non-responder at the second test and responder again at
 the last test. This may of course be a result of methodo-
 logical inconsistency or bad compliance. On the other hand,
 one would expect the status of the platelets in some patients
 to change over time, for instance in relation to changing
 disease activity and related differences in platelet activation

316 pathways. Change in the response to aspirin over time has
317 also been shown by Helgason et al. [6], while Grottemeyer
318 [3] described stability. Both used methods other than PFA-
319 100® to study platelet activity.

320 The clinical results in this subset of patients from the
321 WARIS II trial might indicate that the non-responders are at
322 a higher risk of experiencing a thromboembolic event or of
323 being in need of revascularization. But the numbers are far
324 too small to convey any statistically significant results.

325 Accordingly, we do not yet know whether the phenom-
326 enon of aspirin non-response observed with the PFA-100®
327 has any clinical relevance. This will have to be tested in
328 larger prospective studies on populations using aspirin as
329 the only platelet-inhibiting drug against arterial throm-
330 boembolism. If the observed non-responsiveness to aspirin
331 is shown to be of clinical importance, the PFA-100® seems
332 to be a suitable tool for such testing on routine scale.

333 5. Conclusion

334 Evaluated by the PFA-100® 24 h after the last aspirin
335 intake, a considerable number of post-AMI patients seemed
336 to be non-responders to aspirin in doses of 75 and 160 mg/
337 day with some tendency to dose–response. Circulating
338 levels of P-selectin were also higher in the non-responders
339 compatible with more activated platelets than in the res-
340 ponders. The response seemed to be relatively stable over
341 time. The clinical implications of the observed aspirin non-
342 responsiveness need to be further clarified.

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