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ORIGINAL ARTICLE

A pharmacodynamics comparison of prasugrel and clopidogrel in patients undergoing hemodialysis

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Abstract

Platelet reactivity in the presence of clopidogrel is deteriorated in patients undergoing hemodialysis (HD). However, the impact of residual platelet reactivity with prasugrel use in Japanese patients on HD remains unclear. This was a prospective, multi-center, single-arm study conducted to compare platelet reactivity of prasugrel 3.75 mg per day vs. clopidogrel 75 mg per day in patients on chronic HD. We assessed P2Y12 reaction units (PRU) using the VerifyNow® P2Y12 test for all enrolled patients at baseline (clopidogrel treatment) and at 14 days (prasugrel treatment) pre- and post-HD. Clinical outcomes data were obtained on day 14. A total of 38 patients on HD were included in this study. The PRU were significantly higher in patients on clopidogrel than in patients on prasugrel in both phases (pre-HD: clopidogrel 226 ± 80 vs. prasugrel 175 ± 82, $p < 0.001$) (post-HD: clopidogrel 256 ± 67 vs. prasugrel 210 ± 63, $p < 0.001$). There were no patients with bleeding or adverse events during the two weeks of prasugrel treatment. Prasugrel 3.75 mg per day, adjusted for Japanese patients, inhibited platelet aggregation better than clopidogrel, even after hemodialysis, which might contribute to the reduced incidence of major adverse event in patients undergoing HD.

Keywords High platelet reactivity · Prasugrel · Hemodialysis · Clopidogrel

Abbreviations

HD	Hemodialysis
PRU	P2Y12 reaction unit
DES	Drug-eluting stent
PCI	Percutaneous coronary intervention
LD	Loading dose
MD	Maintenance dose
ACS	Acute coronary syndrome
CAD	Coronary artery disease
HT	Hypertension
DL	Dyslipidemia
DM	Diabetes mellitus
CABG	Coronary artery bypass grafting
EVT	Endovascular treatment
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
DW	Dry weight

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Introduction

Although drug-eluting stents (DES) significantly reduce restenosis compared to bare-metal stents in a wide range of populations [1], hemodialysis (HD) has created a challenge in a subset of patients with massive coronary calcifications and multiple lesions [2]. Despite the initial procedural success and optimal stent expansion with Rotablator® (Boston Scientific, Marlborough, MA, USA) and the scoring balloon, HD is associated with a higher risk of cardiovascular events after DES implantation. Thus, HD is an important risk factor for mortality after percutaneous coronary intervention (PCI) [2–4], and the mechanisms underlying this association are poorly understood.

Recent studies have revealed that high platelet reactivity as measured by the VerifyNow® test (Accriva Diagnostics

Inc., San Diego, CA, USA) is associated with an increased risk of cardiovascular events after DES implantation [5–8]. Several studies have shown that not only end-stage renal dysfunction (ESRD) [9–11], but also HD may lead to high platelet reactivity [12–14]. Notably, platelet reactivity immediately after HD in patients receiving clopidogrel is deteriorated as compared to before HD [15, 16]. We considered that this phenomenon might be one of the mechanisms behind the increase in cardiovascular events after DES implantation in patients undergoing HD.

Prasugrel, a third-generation thienopyridine antiplatelet drug, rapidly and potently inhibits platelet aggregation with less pharmacological variability and similar tolerability compared to other thienopyridines, and was, thus, expected to reduce clinical events after PCI [17]. Actually, the PRASFIT Elective (Prasugrel For Japanese Patients with Coronary Artery Diseases Undergoing Elective PCI) study showed that a prasugrel dosing regimen (LD/MD: 20/3.75 mg) adjusted for Japanese patients with stable coronary artery disease (CAD) undergoing PCI was associated with a low incidence of major adverse cardiovascular events and with a low risk of clinically serious bleeding in patients not on HD [18].

However, a pharmacodynamics comparison of prasugrel and clopidogrel in patients undergoing HD in Japan remains unclear. Therefore, in this study, the primary endpoint was to evaluate platelet reactivity after HD comparing prasugrel and clopidogrel and the aim of this study was to analyze the comparative antiplatelet action of prasugrel 3.75 mg per day vs. clopidogrel 75 mg per day in patients both before and after HD.

Methods

Study population

We performed a prospective, multi-center, single-arm trial to compare platelet inhibition effects of prasugrel 3.75 mg per day to that of 75 mg per day clopidogrel in patients on chronic HD. All patients receiving regular maintenance HD and undergoing chronic treatment with clopidogrel 75 mg per day at a medical institution on Awaji Island were assessed for platelet reactivity using the VerifyNow® P2Y12 test (Accriva) at baseline (clopidogrel treatment) before HD and after HD. Clopidogrel was switched to prasugrel on day 0. Platelet reactivity measurements and safety evaluations were conducted on day 14 (prasugrel treatment). Patient compliance with antiplatelet therapy was assessed via interview and meticulous tablet counting.

All study patients were stable, with no change in their medication or HD conditions during the study, and were undergoing regular maintenance HD for approximately 4 h three times per week. This study was approved by the ethical committee of Hyogo Prefectural Awaji Medical Center, Japan, and all enrolled study patients gave their written informed consent.

Blood sampling (VerifyNow® P2Y12 test (Accriva))

We performed the VerifyNow® P2Y12 test (Accriva) on all enrolled patients at baseline (clopidogrel treatment) and at 14 days after switching clopidogrel treatment to prasugrel treatment before and after HD. Briefly, the VerifyNow® P2Y12 test (Accriva) measures platelet-induced aggregation according to an increase in light transmittance and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU) [19]. The blood before HD was obtained from puncture needle from arterial side of blood access immediately after puncture and that after HD was obtained from most proximal side of the patients from arterial side before removal of the puncture needle.

Short term clinical events

Clinical outcomes data were obtained at the day-14 visit. Cardiac death, myocardial infarction, target lesion revascularization and target vessel revascularization, stent thrombosis, cerebral infarction, and both fatal and non-fatal bleeding were evaluated.

Statistical analysis

The statistical analysis was conducted using SPSS software version 16.0 (SPSS Inc, Chicago, IL). Qualitative data are presented as frequencies, and quantitative data are shown as mean values ± standard deviations (SD). For continuous variables, comparisons between the two groups were performed using a two-tailed paired *t* test or the Wilcoxon test. Discrete variables are presented as percentages, and comparisons were made using the chi-square analysis or Fisher's exact test. A probability value (*p*) of less than 0.05 was considered significant.

Results

Baseline patient characteristics

From August 2014 to December 2015, 38 patients undergoing HD and receiving clopidogrel treatment were included in this study (Fig. 1). Serial PRU using the VerifyNow® (Accriva) were assessed in all enrolled patients (Fig. 2).

The baseline patient characteristics are shown in Table 1. The mean duration of HD was 7.3 ± 6.0 years. The percentages of DM, prior PCI, and prior cerebral infraction were

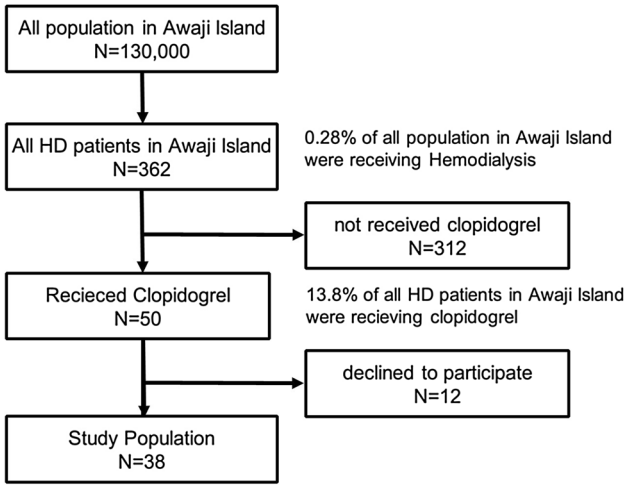

Fig. 1 Flowchart of patients included in the study

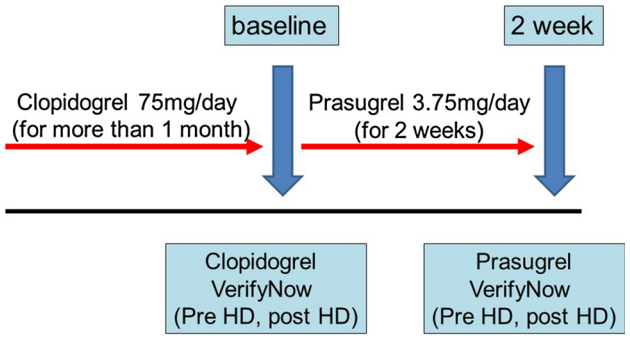

Fig. 2 Study protocol of switching from clopidogrel to prasugrel

52.6%, 76.3% and 10.5%, respectively. The frequencies of patients both clopidogrel and aspirin, cilostazol, or anticoagulant therapy were 73.7%, 36.8% and 5.3%, respectively.

Blood sampling (VerifyNow® P2Y12 test (Accriva))

The efficacies of clopidogrel and prasugrel after HD were significantly decreased compared to before HD (clopidogrel: pre-HD 226 ± 80 vs. post-HD 256 ± 67, $p < 0.001$) (prasugrel: pre-HD 175 ± 82 vs. post-HD 210 ± 63, $p < 0.001$). Furthermore, PRU was significantly higher among patients receiving clopidogrel treatment than among patients receiving prasugrel treatment in both phases (pre HD: clopidogrel 226 ± 80 vs. prasugrel 175 ± 82, $p < 0.001$) (post HD: clopidogrel 256 ± 67 vs. prasugrel 210 ± 63, $p < 0.001$) (Fig. 3).

Short-term clinical events

There were no patients with bleeding or adverse events during the two weeks of prasugrel treatment.

Table 1 Baseline patient characteristics

	Total ($n = 38$)
Age (years)	70.6 ± 8.8
Men, *n* (%)	28 (73.7)
HTN, *n* (%)	33 (86.8)
DM, *n* (%)	20 (52.6)
DL, *n* (%)	19 (50.0)
Prior PCI, *n* (%)	29 (76.3)
Prior CABG, *n* (%)	13 (34.2)
Prior EVT, *n* (%)	14 (36.8)
Prior cerebral infarction, *n* (%)	4 (10.5)
Other antiplatelet therapy, *n* (%)	33 (86.8)
Aspirin, *n* (%)	28 (73.7)
Cilostazol, *n* (%)	14 (36.8)
Anticoagulant therapy, *n* (%)	2 (5.3)
HD duration (years)	7.3 ± 6.0
Dialysis time (h)	4.0 ± 0.4
Vascular access	
AVF, *n* (%)	37 (97.3)
AVG, *n* (%)	1 (2.6)
DW (kg)	57.2 ± 12.7
BMI (kg/m^2)	21.7 ± 3.5
Fluid removal (kg)	1.8 ± 1.1
Fluid removal/DW (%)	3.3 ± 2.0

Values are presented as means ± standard deviations or as numbers of patients (percentages)

HD hemodialysis, *HTN* hypertension, *DL* dyslipidemia, *DM* diabetes mellitus, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *EVT* endovascular treatment, *AVF* arteriovenous fistula, *AVG* arteriovenous graft, *DW* dry weight, *BMI* body mass index

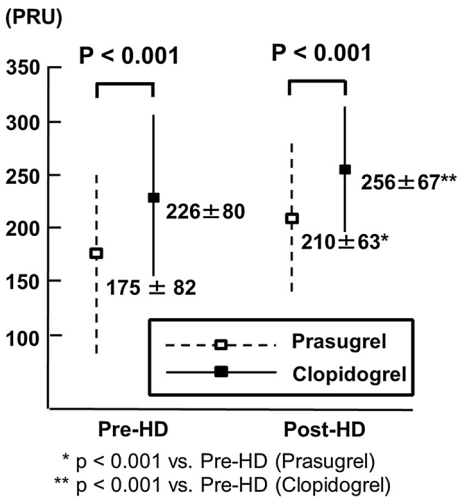

Fig. 3 Time course of the P2Y12 reaction units (PRU) before and after hemodialysis (HD). Comparison of PRU before HD and after HD in patients undergoing HD and receiving both clopidogrel and prasugrel. Values are presented as means ± standard deviations (SD)

Discussion

The present study showed that the efficacies of clopidogrel and prasugrel after HD were significantly decreased compared to before HD, and PRU levels were significantly higher among the patients receiving clopidogrel treatment than among the patients receiving prasugrel treatment in both phases (Fig. 3).

The Japanese Society for Dialysis Therapy reported that the number of patients on HD has still been gradually increasing in Japan and that 0.26% of the entire population were receiving hemodialysis in 2016 (https://docs.jsdt.or.jp/overview/pdf2017/p005.pdf). This number was almost the same as that for the patients on Awaji Island (0.28%) (Fig. 1). In the present study, 13.8% of those patients receiving HD were also taking clopidogrel, and this number was not negligible.

Recent studies have revealed that high platelet reactivity measured by VerifyNow® (Accriva) is associated with cardiovascular events after DES implantation [5–8]. Previous studies revealed that HD itself was a factor in poor responses to clopidogrel [12–14]. High platelet reactivity in patients on HD is caused by the exposure of their blood to the dialyzer membrane [20] or by heparin use [21]. The effect of clopidogrel may be hampered in patients undergoing HD because of an increase in the platelet turnover rate, poor bioavailability, coagulation disorders, extrinsic factors such as uremia and anemia, and a deterioration of the ability to metabolize clopidogrel [13].

Indeed, this study showed that the response to clopidogrel after HD decreased significantly compared to that before HD. Furthermore, the PRU values for clopidogrel after HD were greater than 235–240, which was the optimum cutoff range for the prediction of increased major adverse cardiovascular events [22–25]. Therefore, standard doses of clopidogrel may not fully inhibit platelet reactivity in patients undergoing HD. However, the PRU values for prasugrel 3.75 mg per day were significantly lower compared to those of clopidogrel. The PRU value of prasugrel after HD was 210, which was less than the optimum cutoff range of 235–240. Prasugrel rapidly and potently inhibits platelet aggregation with less pharmacological variability and the 3.75-mg prasugrel dose adjusted for Japanese patients may be expected to reduce clinical events even in patients on HD.

Limitations

The present study has several limitations. First, the detailed information about proton pomp inhibitor such as omeprazole or esomeprazole which could attenuate the effect of antiplatelet therapy, especially clopidogrel, were not collected in the present study. Second, this was an observational study without a power calculation to determine the sample size, which can increase the risk of type 1 error. This prospective study was based on a relatively limited sample size and there were no identified incidences of bleeding, stent thrombosis or cardiac death because of the very short-term clinical follow-up (only 2 weeks). Furthermore, clinical improvement due to the reduction of PRU value after HD remains unclear. Therefore, a larger sample size and a prospective randomized study with long-term clinical follow-up is warranted to prove cause-and-effect relations.

Conclusion

Prasugrel 3.75 mg per day adjusted for Japanese patients inhibits platelet aggregation in comparison with clopidogrel even after hemodialysis, which might contribute to reduce the incidence of major adverse event in patients with HD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no potential conflicts of interest.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R (2002) A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 346:1773–1780
2. Otsuka Y, Ishiwata S, Inada T, Kanno H, Kyo E, Hayashi Y, Fujita H, Michishita I (2011) Comparison of haemodialysis patients and non-haemodialysis patients with respect to clinical characteristics and 3-year clinical outcomes after sirolimus-eluting stent implantation: insights from the Japan multi-centre post-marketing surveillance registry. Eur Heart J 32:829–837
3. Ikari Y, Tanabe K, Koyama Y, Kozuma K, Sano K, Isshiki T, Katsuki T, Kimura K, Yamane M, Takahashi N, Hibi K, Hasegawa K, Ishiwata S, Kiyooka T, Yokoi H, Uehara Y, Hara K (2012) Sirolimus eluting coronary stent implantation in patients on maintenance hemodialysis: the OUCH study (outcome of cypher stent inhemodialysis patients). Circ J 76:1856–1863
4. Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T, Mitsudo K, Miyazaki S, Yamaguchi T, Hiyoshi E, Nishimura E, Isshiki T, Investigators R (2010) Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: observations from the Registry of Stent

Thrombosis for Review and Reevaluation (RESTART). Circulation 122:52–61
5. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD, Investigators A-D (2013) Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 382:614–623
6. Angiolillo DJ, Bernardo E, Sabate M, Jimenez-Quevedo P, Costa MA, Palazuelos J, Hernandez-Antolin R, Moreno R, Escaned J, Alfonso F, Banuelos C, Guzman LA, Bass TA, Macaya C, Fernandez-Ortiz A (2007) Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 50:1541–1547
7. Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, Patti G, Breet NJ, DiSciascio G, Cuisset T, Dangas G (2011) Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol 58:1945–1954
8. Konishi A, Shinke T, Otake H, Nishio R, Sawada T, Takaya T, Nakagawa M, Osue T, Taniguchi Y, Iwasaki M, Kinutani H, Masaru K, Takahashi H, Terashita D, Shite J, Hirata K (2015) Impact of cytochrome P450 2C19 loss-of-function polymorphism on intra-stent thrombi and lesion outcome after everolimus-eluting stent implantation compared to that after first-generation drug-eluting stent implantation. Int J Cardiol 179:476–483
9. Park SH, Kim W, Park CS, Kang WY, Hwang SH, Kim W (2009) A comparison of clopidogrel responsiveness in patients with versus without chronic renal failure. Am J Cardiol 104:1292–1295
10. Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabate M, Ferreiro JL, Ueno M, Jimenez-Quevedo P, Alfonso F, Bass TA, Macaya C, Fernandez-Ortiz A (2010) Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. J Am Coll Cardiol 55:1139–1146
11. Geisler T, Grass D, Bigalke B, Stellos K, Drosch T, Dietz K, Herdeg C, Gawaz M (2008) The Residual Platelet Aggregation after Deployment of Intracoronary Stent (PREDICT) score. J Thromb Haemost 6:54–61
12. Woo JS, Kim W, Lee SR, Jung KH, Kim WS, Lew JH, Lee TW, Lim CK (2011) Platelet reactivity in patients with chronic kidney disease receiving adjunctive cilostazol compared with a high-maintenance dose of clopidogrel: results of the effect of platelet inhibition according to clopidogrel dose in patients with chronic kidney disease (PIANO-2 CKD) randomized study. Am Heart J 162:1018–1025
13. Alexopoulos D, Panagiotou A, Xanthopoulou I, Komninakis D, Kassimis G, Davlouros P, Fourtounas C, Goumenos D (2011) Antiplatelet effects of prasugrel vs. double clopidogrel in patients on hemodialysis and with high on-treatment platelet reactivity. J Thromb Haemost 9:2379–2385
14. van Bladel ER, de Jager RL, Walter D, Cornelissen L, Gaillard CA, Boven LA, Roest M, Fijnheer R (2012) Platelets of patients with chronic kidney disease demonstrate deficient platelet reactivity in vitro. BMC Nephrol 13:127
15. Konishi A, Shinke T, Otake H, Takaya T, Osue T, Kinutani H, Kuroda M, Takahashi H, Terashita D, Hirata K (2016) Impact of residual platelet reactivity under clopidogrel treatment for lesions and the clinical outcome after drug-eluting stent implantation in patients with hemodialysis. J Cardiol 67:531–537
16. Konishi A, Shinke T, Otake H, Nakatani D, Nakagawa M, Inoue T, Hariki H, Osue T, Taniguchi Y, Iwasaki M, Nishio R, Hiranuma N, Kinutani H, Kuroda M, Shite J, Hirata K (2014) Impact of hemodialysis on local vessel healing and thrombus formation after drug-eluting stent implantation. J Cardiol 64:25–31
17. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, Investigators T-T (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357:2001–2015
18. Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, Kitagawa K, Nishikawa M, Miyazaki S, Ikeda Y, Nakamura M, Saito S, Investigators PR-E (2014) Prasugrel, a third-generation P2Y12 receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. Circ J 78:2926–2934
19. Malinin A, Pokov A, Spergling M, Defranco A, Schwartz K, Schwartz D, Mahmud E, Atar D, Serebruany V (2007) Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12(R) rapid analyzer: the VERIfy Thrombosis risk ASsessment (VERITAS) study. Thromb Res 119:277–284
20. Aggarwal A, Kabbani SS, Rimmer JM, Gennari FJ, Taatjes DJ, Sobel BE, Schneider DJ (2002) Biphasic effects of hemodialysis on platelet reactivity in patients with end-stage renal disease: a potential contributor to cardiovascular risk. Am J Kidney Dis 40:315–322
21. Gritters M, Borgdorff P, Grooteman MP, Schoorl M, Schoorl M, Bartels PC, Tangelder GJ, Nube MJ (2008) Platelet activation in clinical haemodialysis: LMWH as a major contributor to bioincompatibility? Nephrol Dial Transplant 23:2911–2917
22. Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, Buonamici P, Antoniucci D, Abbate R, Gensini GF (2009) Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 119:237–242
23. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, Deneer VH, Harmsze AM, van der Heyden JA, Rensing BJ, Suttorp MJ, Hackeng CM, ten Berg JM (2010) Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 303:754–762
24. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, Bhatt DL, Cattaneo M, Collet JP, Cuisset T, Gachet C, Montalescot G, Jennings LK, Kereiakes D, Sibbing D, Trenk D, Van Werkum JW, Paganelli F, Price MJ, Waksman R, Gurbel PA, Working Group on High On-Treatment Platelet R (2010) Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 56:919–933
25. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, Dick A, Marquis JF, O'Brien E, Goncalves S, Druce I, Stewart A, Gollob MH, So DY (2012) Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet 379:1705–1711