Value of platelet pharmacogenetics in common clinical practice of patients with ST-segment elevation myocardial infarction☆

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A B S T R A C T

Background: Antiplatelet drug resistance is a well-known problem, causing recurrent cardiovascular events. Multiple genetic polymorphisms have been related to antiplatelet resistance by several large trials, however data from common clinical practice is limited. We examined the influence of previously described polymorphisms, related to aspirin and clopidogrel resistance, on treatment outcome in a real life unselected population of patients presenting with ST-segment elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention.

Methods and results: This cohort study consisted of 1327 patients with STEMI. Patients were treated according to a standardized guideline-based protocol. Nine polymorphisms, COX1 (−842A>G), P2Y1 (893C>T), GPIa (807C>T), GPIIa (PAI1/A2), CYP2C19 (*2, *3 and *17), ABCB1 (3435T>C) and PON1 (576A>G), were genotyped. During 1 year of follow up the primary endpoint, a composite of cardiac death or recurrent myocardial infarction, was reached in 86 patients. The COX1 and CYP2C19*2 polymorphisms were associated with the primary endpoint, HR 2.55 (95% CI 1.48–4.40), P=0.001 and HR 2.03 (1.34–3.09) P=0.001, respectively. The combined analysis demonstrated a 2.5-fold increased risk for individuals with ≥2 risk alleles, P = 6.9 × 10−5. The association of COX1 was driven by mortality related events whereas that of CYP2C19*2 was mainly attributed to myocardial infarction and stent thrombosis.

Conclusion: In this unselected, real life population of STEMI patient on dual-antiplatelet therapy, the polymorphisms COX1 −842A>G and CYP2C19*2 were determinants of thrombotic complications during follow-up. We show that in a clinical setting, testing for these polymorphisms could be of value in the identification of STEMI patients at risk for recurrent cardiovascular events.

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1. Introduction

Insufficient platelet inhibition during adequate guideline antiplatelet therapy is a well-known problem in the secondary prevention of coronary artery disease, causing a considerable amount of patients to suffer from recurrent thrombotic events [1]. Individual differences in the intrinsic rate of platelet reactivity and variability in response to antiplatelet therapy are the main underlying mechanisms responsible for this so-called antiplatelet therapy resistance. For both aspirin and clopidogrel this problem has been recognized. Several factors play a role in this inadequate response to antiplatelet agents. Clinical factors like increased body mass index (BMI), diabetes mellitus and drug–drug interactions have been implicated [1]. Moreover, genetic polymorphisms causing individual variability in drug absorption, metabolism and availability of biological targets, like platelet receptors, influence the platelet inhibition during therapy in each individual [1].

Pharmacogenetics is the upcoming field of research exploring the influence of genetic variation on response to drug therapy, to pursue...
achievement of individualized therapy. There is growing evidence that aspirin- and especially clopidogrel resistance are partially determined by carrying risk alleles of several single nucleotide polymorphisms (SNPs) in genes resulting in altered drug efficacy [1]. In comparison with the largely inconsistent pharmacogenetic evidence on aspirin resistance due to high variability in laboratory tests and the small sample size of most studies [2], clopidogrel pharmacogenetics has become a well-recognized risk factor for resistance to treatment. Over the last years, multiple studies consistently reported an association of the reduced-function alleles of CYP2C19 and clopidogrel resistance and occurrence of thrombotic events [3–5]. However, the most recent meta-analyses did not demonstrate this association [6,7]. The studies included in these analyses comprise several patient groups, including patients with stable and unstable angina and the spectrum acute coronary syndromes. Specific data on patients with ST-segment elevation myocardial infarction (STEMI), a subpopulation specifically at high risk for thrombotic events, is limited. Furthermore, data on the generalizability of this evidence to the patients seen in the daily clinical practices is largely lacking.

The only large population based study on this subject is that of Simon et al. in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) population (n=2208) [8]. Although this well-designed study investigated probably a good representative population, they still applied several exclusion criteria such as pre-specified levels of biomarkers and duration of complaints. Moreover, of the total included population, only 53% were STEMI patients and only 70% of the patients were treated with percutaneous coronary intervention (PCI), making it a quite heterogeneous population. Also the genotypic analysis was limited to 4 candidate genes. All other cohort studies were smaller and had even less patients with STEMI [9–11].

To obtain answers on the role of pharmacogenetics in the outcome of patients suffering from STEMI, our study investigated the effect of the best described polymorphisms implicated in antiplatelet therapy efficacy on thrombotic complications in a prospectively gathered real life unselected population of patients presenting with STEMI. The goal was to evaluate whether the described effects of these polymorphisms were detectable in this high risk population and could therefore possibly be of value for application in the common clinical practice.

2. Methods

2.1. Study population

The population of the current study consists of patients who were admitted with the diagnosis STEMI to the Leiden University Medical Center (LUMC), Leiden, The Netherlands, between February 2004 and January 2010. All patients underwent primary PCI and were treated according to the previously described standardized guideline-based MISSION AMI care program [12]. In brief, the protocol includes a pre-hospital triage system based on 12-lead electrocardiography and when eligible pre-hospital administration of aspirin (300 mg), clopidogrel (600 mg) and abciximab (25 μg/kg bolus, followed by 10 μg/kg/min for 12 h) was performed to pursue early reperfusion. Patients were directly transferred to the catheterization laboratory for primary PCI. Beta-blockers and angiotensin-converting enzyme (ACE) inhibitors were titrated to achieve an optimal heart rate and blood pressure control. Moreover, statin treatment was started in all patients. Patients without complications were discharged at day 3 after education on lifestyle changes and drug compliance. Aspirin (100 mg/day) was prescribed indefinitely, and clopidogrel (75 mg/day) for 12 months, irrespective of implanted stent type. All patients were offered an outpatient rehabilitation program.

2.2. Follow-up and study endpoints

During the first year, 4 outpatient clinic visits were scheduled. During this 1 year of follow-up all thrombotic cardiovascular events were recorded. In this study, the primary endpoint was the composite of cardiac death and recurrent myocardial infarction (MI). Secondary endpoints included cardiac death and MI separately, as well as definite stent thrombosis, repeat revascularization and all-cause mortality. All deaths were defined as cardiac, unless clearly proven non-cardiac. Myocardial infarction was defined as a troponin T level above the upper limit in the presence of ischemic complaints or PCI or a re-rise of >25% after recent MI in the presence of symptoms or PCI. Stent thrombosis was defined as angiographic or pathological confirmation of a partial or total thrombotic occlusion within the stent or 5 mm proximally or distally to the stent [13]. Finally, data on revascularization of any coronary artery, irrespective of the treatment modality (PCI or CABG) was collected. Target vessel revascularizations were all clinically driven.

2.3. Genotyping

EDTA blood was prospectively collected on admission and DNA was extracted following standard procedures. DNA was available from 1370 of the 1674 consecutive patients. Reasons for missing DNA were death before the collection of blood or failure of the DNA extraction.

The most well replicated genetic polymorphisms related to aspirin and clopidogrel resistance were selected after a systematic search of literature, as described previously [1]. In brief, relevant articles were identified by searching MEDLINE using keywords and Medical Subject Headings (MeSH) terms including the following: pharmacogenetics, single nucleotide polymorphism, treatment outcome, adverse effects, drug therapy and cardiovascular disease (CVD). All available literature until May 2011 was included and reviews, editorials, and articles in languages other than English were excluded. A multiplex assay was designed using Assay designer software. When a SNP did not fit the multiplex, a proxy of that SNP was selected with the highest R² value. The final set included cyclooxygenase 1 (COX1) –842A>G (rs10306114), P2Y12 receptor (P2Y12) 893C>T (rs1065776), P2Y12 52C>G (rs8608969), glycoprotein (GP) IIb/IIIa receptor (GP IIb/IIIa) 807C>T (rs1126643), GM12890T (in complete linkage disequilibrium (LD) (R² = 1.0) with R2A/A2 [rs5918]), cytochrome P450 (CYP) 2C19*2 [rs4244285], CYP2C19*17 [rs4986899], granzyme B (GZMB) 52G>T (rs11188072) (in complete LD (R² = 1.0) with CYP2C19*17 [rs12245856]), ATP-binding cassette sub-family B member 8 (ABCB1) [rs2235048] (as a proxy for 3435T>C [rs1045642], in complete LD with R² = 1.0) and paraoxonase-1 (PON1) 576A>G (rs562) (Supplementary Table 1).

These SNPs, except the SNP in PON1, were genotyped by MALDI-TOF mass spectrometry, using the MassARRAY™ methodology (Sequenom Inc., San Diego, CA, USA), following the manufacturer’s instructions. The PON1 576A>G (rs562) SNP was genotyped using a TaqMan drug metabolism genotyping assay (Assay ID C_2548962_20; Applied Biosystems, Foster City, CA, USA). As quality control, 5% of the samples were genotyped in duplo. No inconsistencies were observed. All the negative controls (2%) were negative. Call rate of all SNPs was above 98%. Two SNPs deviated significantly from Hardy–Weinberg (HW) equilibrium. P2Y12 52C>G (rs8609699) (HW ChiSq 362.7, P = 7.4x 10⁻¹⁵) was excluded from further analysis. The CYP2C19*3 polymorphism (HW ChiSq 640, P = 1.3x 10⁻⁴) was included, since the deviation was caused by 1 homozygote of the minor allele of this low frequency SNP (0.3% in the current population). This minor allele frequency was lower than the reported frequency in HapMap CEU reference panel (1.7%) (http://www.hapmap.org). All other SNPs matched with the reported frequencies. Finally, individuals with 50% or more failed SNPs were excluded (3%), the final analysis included 1327 patients.

3. Statistics

To compare the group with and the group without a primary outcome event, categorical parameters are compared with Pearson chi-square or Fisher’s exact test when appropriate. Continuous data were compared with unpaired 2-sided Student’s t-test. In the case of non-Gaussian distribution, variables were compared with the Mann–Whitney test. All SNPs were tested for deviation from Hardy–Weinberg equilibrium using chi-square analysis.

Associations of SNPs with outcome events were calculated using multivariable, stepwise, forward Cox analyses assuming an additive genetic model. This multivariable model included the clinical variables that were significantly different between the primary event group and the group without. For the polymorphisms associated with P<0.05, recessive and dominant models were tested. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

4. Results

4.1. Baseline characteristics

All patients were treated with a primary PCI and received dual antiplatelet therapy with aspirin and clopidogrel. In-hospital mortality of the final study population was 1.8% (24 patients). At discharge from the hospital admission following the primary intervention, aspirin and clopidogrel were prescribed to 96.0% and 99.7% of the patients.
patients respectively. However, all patients received the loading of clopidogrel.

During follow-up 86 patients (6.5%) reached the primary composite endpoint consisting of cardiac death or recurrent myocardial infarction. A total of 57 patients (4.3%) died, of which 48 of a cardiac cause. Forty-four patients (3.3%) suffered from a recurrent myocardial infarction and 237 patients (17.9%) required repeat revascularization, of which 72 (30.3% of all revascularizations) were treated for an acute indication like unstable complaints or MI. Ninety-two procedures (6.9% of all patients) were revascularizations of the target vessel.

Stent thrombosis was recorded in 15 patients (1.1%). Several baseline and procedural characteristics were significantly different between the primary endpoint group and the patients without the primary endpoint (Table 1). The event group was older, more likely to have hypertension, diabetes mellitus and a previous myocardial infarction in their medical history, but less likely to have a positive family history for cardiovascular disease. The location of the culprit lesion in the right coronary artery (RCA) was less often found in the primary event group, whereas it was more frequent in the left main (LM) coronary artery. The patients with a primary event were more often found to have multivessel disease and had a higher Killip class. The type of the implanted stent was also associated with clinical outcome events. Patients receiving drug-eluting stents (DES) had a lower risk of an event. Moreover, during the primary intervention, in the event group more patients suffered from cardiac shock requiring medical intervention and the classification of the final TIMI flow after the intervention was lower compared to the group without an event. Aspirin and beta-blockers were less frequently prescribed at discharge to the patients that suffered from a primary event during follow up.

4.2. Genotypic analysis

Of the 9 SNPs that were analyzed, the COX1 −842A>G polymorphism and the CYP2C19*2 reduced-function polymorphism were significantly associated with the primary endpoint (Table 2). For both SNPs there was an increase in the hazard ratio for an outcome event during follow-up compared to carriage of 0 or 1 reduced function alleles (20.5% versus 6.0%; adjusted hazard ratio 2.38, 95% CI 1.36–4.17, P=0.003). The recessive genetic model proved to be the most appropriate for analysis of the COX1 SNP. When considering both SNPs together, 779 (59%) patients were homozygote for the wild type alleles of both SNPs, 435 (33%) patients had 1 risk allele, 87 (7%) patients had 2 risk alleles and 8 (1%) patients were carrying 3 risk alleles. In our population no patient was homozygote for both variant alleles of both SNPs. Compared to the patients with 0 or 1 risk allele, the patients who were carrying 2 or 3 risk alleles had an increased risk of the primary endpoint, HR 2.57 (95% CI 1.87–3.54), P=6.9 × 10^{-9}. Analysis of the different stent type groups did not result in different results than the analysis of the total study population. Univariable analysis of the patients receiving BMS (N=415) did not result in significant associations of the COX1 SNP (P=0.093) and CYP2C19*2 (P=0.13) with the primary endpoint, whereas combination of these 2 SNPs did demonstrate a significant association (P=0.004).

These three analyses did show significant associations in the DES subgroup (N=843), P=0.021 for COX1 −842A>G, P=5.4 × 10^{-5} for CYP2C19*2 and P=9.3 × 10^{-5} for the combined analysis.

When analyzing the outcome events such as death, recurrent MI, repeat revascularization and stent thrombosis separately, the COX1 SNP was demonstrated to have a strong association with the mortality related endpoints. However, no significant association was found with the thrombotic endpoints such as myocardial infarction and stent thrombosis, P=0.20 and P=0.59 respectively.

In contrast, the CYP2C19*2 polymorphism was associated with all endpoints, except for the mortality related endpoints (Fig. 3). Patients with the homozygote variant genotype of this SNP were especially at risk for myocardial infarction, HR 2.76 (95% CI 1.73–4.41), P=2.3 × 10^{-5} and stent thrombosis, HR 4.82 (95% CI 2.42–9.59), P=7.7 × 10^{-6}. In
addition, a significant relation was also found with the different repeat revascularization related endpoints.

### 5. Discussion

The key finding of this study is that in this unselected real life population of STEMI patients treated with PCI, the homozygous variant genotype of the CYP2C19*2 polymorphism is a strong determinant of the occurrence of thrombotic events during the first year of follow-up. In addition, the −842A>G polymorphism of COX1 is associated with the composite endpoint of cardiac death and recurrent myocardial infarction as well. Especially patients carrying 2 or more risk alleles of these 2 SNPs were at high risk. None of the other previously reported SNPs with proposed pharmacogenetic influence of antiplatelet therapy efficacy were associated with outcome events during 1 year follow-up after STEMI.

The vast amount of pharmacogenetic research of the last years resulted in a tremendous increase of knowledge on pharmacogenetic gene–drug interactions, however inconsistent results prevented reaching consensus and moving the field forward to clinical application. Even regarding the CYP2C19*2 polymorphism, the major enzyme involved in the metabolic conversion of the clopidogrel prodrug into its active form [2], that was thought to have a significant role in the outcome of patients treated with clopidogrel, recent meta-analyses report conflicting results [3,6,7]. The current study demonstrates that this SNP and the COX1 polymorphism are significant determinants of thrombotic events in an unselected real life population of patients presenting with STEMI.

Cyclooxygenase 1 (COX1, or prostaglandin endoperoxide G/H synthase) catalyzes the metabolism of arachidonic acid to prostaglandin H2, which is subsequently metabolized to thromboxane A2. This enzyme is the therapeutic target of aspirin [14]. The −842A>G polymorphism, that is in complete linkage disequilibrium with 50C>T, was first described by Halushka et al. as a determinant of aspirin responsiveness in healthy individuals. However, subsequent studies investigating patient populations were largely inconsistent [15–19]. To date, the only studies that investigated the association of −842A>G or 50C>T with clinical events did not find a significant relation [20,21]. The association of −842A>G with the primary endpoint of the current study appears to be caused by the strong relation with mortality and not with myocardial infarction. The exact mechanism of this relation is unclear, since a causal relation between mortality and aspirin resistance in the absence of an association with myocardial infarction seems unlikely.

Data on genetic variation associated with aspirin resistance comes only from studies with small sample sizes (<500 subjects) and when considering the small effect size of the individual SNPs and the variability of laboratory tests for aspirin resistance [22], it is not surprising that the reported results are largely inconsistent [16,17,20,23–26]. In the current study only COX1 −842A>G was shown to have a significant association with the primary endpoint. But as stated above, this effect seems to be driven by an increased risk of mortality of carriers of this SNP and not due to the more thrombotic specific endpoint myocardial infarction or stent thrombosis. However, even if an effect of a specific SNP on aspirin efficacy exists, it is likely that it will not be detectable in this population with dual antiplatelet therapy since the decreased antiplatelet inhibition will be overcome by the concomitant use of clopidogrel.

In contrast with the COX1 SNP, the association of CYP2C19*2 with the primary endpoint is determined by its effect on the risk of recurrent myocardial infarction and not on cardiac death. Unlike the controversy of its relation with cardiovascular events, the reduced platelet inhibition by clopidogel in carriers of the reduced function of the CYP2C19 polymorphism has been clearly demonstrated in several clinical trials [27,28]. The mechanism of this effect is likely related to a reduced metabolism of clopidogrel prodrug to its active metabolite, thus reducing the platelet inhibition by clopidogel to the level of aspirin alone [29]. This effect has been confirmed in several studies [30,31], and is predicted by the observed polymorphism in the CYP2C19 gene [32].
alleles is not questioned [7], making it likely that this is the causal mechanism of the relation with events found in the current study. In addition, patients that carry risk alleles for both of these SNPs are especially at risk as is shown by the combined risk analysis.

Early 2011, a SNP in the paraoxonase-1 gene, 576A>G (R192Q), was described as the major determinant of clopidogrel efficacy in platelet inhibition as well as stent thrombosis [27], instead of CYP2C19*2. However, since then, several study groups failed to confirm these findings in other cohorts [28–30]. Also in the current STEMI population no association between the PON1 genotype and cardiovascular events could be demonstrated.

The results of the current study demonstrate the strong effect of the CYP2C19*2 polymorphism and the increased risk of thrombotic complications during 1 year of follow-up after presenting with STEMI. The question remains how this knowledge can contribute to the improvement of the treatment outcome of these patients. Initially it was thought that increasing the dose of clopidogrel in patients with insufficient platelet inhibition on a normal dose of clopidogrel might improve the outcome [31]. The results of the Gauging Responsiveness with A Verifynow assay—Impact on Thrombosis And Safety (GRAVITAS) trial could not endorse this hypothesis, probably because of the fact that also a higher dose of clopidogrel does not lead to significant platelet inhibition in these patients [32]. In the ELEVATE-TIMI 56 (Escalating Clopidogrel by Involving a Genetic Strategy — Thrombolysis In Myocardial Infarction 56), Mega et al. demonstrated that after tripling the clopidogrel dose to 225 mg daily in CYP2C19*2 heterozygotes did achieve levels of platelet inhibition comparable to that seen with the standard 75 mg dose in non-carriers. However in the *2 homozygotes even 300 mg clopidogrel did not result in adequate platelet inhibition [33]. In addition, similar results with respect to clinical events were reported by the REsponsiveness to CLOpidogrel and Stent-related Events-2 in Acute Coronary Syndromes (RECLOSE-2 ACS) study [34]. Patients with high residual platelet activity had an increased event risk compared to those with low platelet activity after clopidogrel loading, despite increasing the clopidogrel dose or switching to ticlopidine [34].

Recently, genetic substudies of the TRITON-TIMI-38 [35] and PLATO (PLATelet inhibition and patient Outcomes) [36] trials, investigating the more potent prasugrel and ticagrelor, respectively, have demonstrated that these agents are not significantly affected by the genetic variation in the CYP2C19 gene nor in other described genes. Prescribing one of these drugs to all patients probably would solve almost all of the pharmacogenetic problems, since the relative small effects of the SNPs are overbalanced by the much stronger platelet inhibition of these drugs. However,
subsequent additional bleeding complications should be weighed against the benefit of these drugs, especially in individuals already at risk for bleeding complications. A well-validated score for estimating bleeding risk is however lacking [37]. In the latest guidelines on myocardial revascularization by the European Society of Cardiology the recommended antiplatelet therapy for STEMI patients consists of dual antiplatelet therapy with aspirin and prasugrel or ticagrelor. In this guideline, clopidogrel should only be used in the more effective platelet inhibitors that are contraindicated or unavailable [37]. Nevertheless, an attractive application of the pharmacogenetic knowledge of CYP2C19 could be genotypic guidance in the choice of prescribing clopidogrel to patients with 0 or 1 reduced-function allele of CYP2C19 and prasugrel or ticagrelor to the carriers of 2 variant alleles [38]. Clinical benefit of this theory as well as economic cost-effectiveness remains to be proven by currently on-going trials (for instance ReAssessment of Anti-Platelet Therapy Using an iNdividualized Strategy Based on GENEtic Evaluation [RAPID GENE, NCT01184300], Thrombocyte Activity Reassessment and GENoTyping for PCI [TARGET-PCI, NCT01177592] and Genotyping Infarct patients to Adjust and Normalize Thienopyridine treatment [GIANT, NCT01134380]).

The results of the first study were presented at the Transcatheter Cardiovascular Therapeutics (TCT) congress 2011. In the RAPID GENE study 200 patients were randomized to a treatment strategy genotyping and prasugrel prescription for CYP2C19*2 carriers, or to standard therapy with clopidogrel. The authors demonstrated that treatment with prasugrel completely eliminated HPR in the CYP2C19*2 carriers compared to treatment with clopidogrel (unpublished results). Whether this strategy is also cost-effective compared to prasugrel prescription to all patients and if the rate of bleeding complication is lower remains to be shown.

6. Limitations

Some limitations of this study are worthwhile being mentioned. The fact that all patients in our population received dual antiplatelet therapy limits the possibility to investigate a true pharmacogenetic effect of these SNPs, since there is no placebo controlled group to compare with. Therefore, the relation we detected could theoretically be a direct relation between the SNP and the thrombotic events, independent of the antiplatelet therapy. However a recent meta-analysis of several genome wide associations studies on coronary artery disease did not detect any of the SNPs from the current study [39], making the chance of an antiplatelet drug independent association unlikely. No platelet function tests were performed in the current study. In the current study three CYP2C19 alleles (*2, *3 and *17 respectively) were analyzed. Although, other alleles in this gene and in other CYP genes have also been associated with clopidogrel metabolism [35], we decided not to analyze these SNPs considering the low allele frequency of some of these SNPs and because the evidence of their involvement is not that solid as compared to the three CYP SNPs tested in the current study [2]. The observational nature of our study could be seen as a limitation. However, to determine the clinical value of findings derived from earlier large trials in an unselected and clinically representative patient population can provide important additional value. Our population is suitable for this purpose for several reasons. First, since we did not handle exclusion criteria on the type or duration of STEMI nor on the subsequent therapy, our cohort is a good representation of common clinical practice. Second, since all patients were treated according to the standardized guideline-based MISSION! protocol, possible confounding factors during the follow-up period are kept to a minimum.

7. Conclusion

The contribution to the existing evidence of the current study is that it demonstrates that in daily clinical practice of patients with STEMI, of all the previously proposed candidate SNPs involved in platelet pharmacogenetics, only the influence of the COX1 — 842A>G and CYP2C19*2 polymorphisms on the 1 year combined thrombotic outcome could be demonstrated and seems of clinical significance. Considering the population size this does not imply that the other genetic markers are not associated with antiplatelet treatment failure, but that their possible influence is so small that it is unlikely that they are of clinical relevance. The mortality driven association with COX1 — 842A>G deserved further research in a study more specifically dedicated to this endpoint. On-going studies on pharmacogenetic guidance of antiplatelet therapy using the CYP2C19 reduced function alleles will provide answers whether this strategy can contribute to finding the balance between adequate platelet inhibition and avoidance of excessive bleeding risk.

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Conflict of interest

J.W.J. was a speaker on (CME accredited) meetings sponsored by Astellas, Astra-Zeneca, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Genzyme, Medtronic, Merck-Schering-Plough, Pfizer, Orbis Neich, Novartis, Roche, Servier and Sanofi Aventis.

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