Cardiology News /Recent Literature Review / Mid Quarter 2012

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The **ESC** Congress will be held in Munich, 25-29/8/2012

TCT Meeting will take place in Miami, 22-26/10/12

HCS Meeting to be held in Athens, 1-3/11/12

AHA 2012 is scheduled for Los Angeles, 3-7/11/12

TWENTE Trial: the Resolute Zotarolimus Eluting Stents are Noninferior to Xience V Everolimus Eluting Stents in Treating "Real-World" Patients with Complex Lesions and "Off-label" Indications for DES

A total of 1,391 patients were randomly assigned to zotarolimus eluting stents (ZES) (n = 697) or everolimus eluting stents (EES) (n = 694). Acute coronary syndromes were present in 52% and "off-label" feature in 77% of patients. Of the lesions, 70% were type B2/C; the post-dilation rate was very high (82%). In ZES and EES, target vessel failure (TVF) occurred in 8.2% and 8.1%, respectively (absolute risk-difference 0.1%; p (noninferiority) = 0.001). The definite-or-probable stent thrombosis rates were relatively low and similar for ZES and EES (0.9% and 1.2%, respectively, p = NS). Definite stent thrombosis rates were also low (0.58% and 0%, respectively, p = NS). In EES, probable stent thrombosis beyond day 8 was observed only in patients not adhering to dual antiplatelet therapy. The authors concluded that resolute ZES were noninferior to Xience V EES in treating "real-world" patients with a vast majority of complex lesions and "off-label" indications for drug-eluting stents (DES), which were implanted with liberal use of post-dilation (von Birgelen C et al, *J Am Coll Cardiol* 2012;59:1350–1361).

The TARGET Study: Placement of the LV Lead to the Latest Sites of Contraction and Away from the Scar Confers the Best Response to CRT

Among 220 patients receiving cardiac resynchronization therapy (CRT), the left ventricular (LV) lead was positioned at the latest site of peak contraction (as determined by echocardiographic speckle-tracking 2-dimensional radial strain imaging) with an amplitude of >10% to signify freedom from scar (n=110, TARGET group), while in the control group (n=110) standard unguided CRT was performed. In the TARGET group, there was a greater proportion of responders at 6 months (70% vs 55%, p = 0.031) with an absolute difference in the primary endpoint ($\geq$15% reduction in LV end-systolic volume at 6 months) of 15%. Compared with controls, TARGET patients had a higher clinical response (83% vs 65%, p = 0.003) and lower rates of the combined endpoint (all-cause mortality and heart failure–related hospitalization) (p = 0.031). The authors concluded that compared with standard CRT treatment, the use of speckle-tracking echocardiography to the target LV lead placement yields significantly improved response and clinical status and lower rates of combined death and heart failure–related hospitalization (Khan FZ et al, ***J Am Coll Cardiol*** 2012;59:1509–1518).

EMPHASIS-HF: In Patients with Systolic Heart Failure and Mild Symptoms, Eplerenone Reduced the Incidence of New Onset AF/AFlu

Patients in New York Heart Association functional class II heart failure (HF) and with ejection fraction $\leq$35% were eligible for EMPHASIS-HF. New onset atrial fibrillation or flutter (AFF) was significantly reduced by eplerenone: 25 of 911 (2.7%) vs 40 of 883 (4.5%) in the placebo group (hazard ratio -HR: 0.58; p = 0.034). The reduction in the primary endpoint (cardiovascular mortality or hospitalization for HF) with eplerenone was similar among patients with and without AFF at baseline (HR: 0.60 vs. HR: 0.70, respectively; p for interaction = NS). The primary endpoint, was not significantly different in subjects with and without AFF at baseline (both study groups combined: HR: 1.23; p = 0.33). The authors concluded thatiIn patients with systolic heart failure and mild symptoms, eplerenone reduced the incidence of new onset AFF. The effects of eplerenone on the reduction of major CV events were similar in patients with and without AFF at baseline (Swedberg K et al, ***J Am Coll Cardiol*** 2012;59:1598–1603).

ACUITY Trial: Although Infrequent, Intraprocedural Thrombotic Events in Patients Undergoing Early PCI for NSTE Acute Coronary Syndrome are Strongly Associated with Subsequent Adverse Outcomes

Among 3,428 patients undergoing PCI for non–ST-segment elevation acute coronary syndrome, an intraprocedural thrombotic event (IPTE) (new or increasing thrombus, abrupt vessel closure, no reflow, slow reflow, or distal embolization) occurred in 121 patients (3.5%). Patients with IPTE had higher in-hospital, 30-day, and 1-year major adverse cardiac event rates than patients without IPTE (25.6% vs 6.3% in-hospital, 30.6% vs 9.3% at 30 days, and 37.0% vs. 20.5% at 1 year; p <0.0001 for each). An IPTE was strongly associated with Q-wave myocardial infarction and stent thrombosis (in-hospital 3.3% vs. 0.5%, p = 0.006; 30 days 5.8% vs. 1.3%, p < 0.0001; and 1 year 6.7% vs.

2.0%, p = 0.0002). Unplanned or target vessel revascularization, and major bleeding were also increased among patients with IPTE, as was overall 30-day mortality (3.3% vs. 0.7%, p = 0.002). The authors concluded that, although infrequent, IPTE was associated with subsequent adverse outcomes including death, myocardial infarction, and stent thrombosis (McEntegart MB et al, ***J Am Coll Cardiol*** 2012;59:1745–1751).

HORIZONS-AMI Trial: Mortality and Major Bleeding are Higher After In-hospital Compared with Out-of-hospital Stent Thrombosis

Over 3 years, stent thrombosis developed in 156 (4.9%) of 3,202 STEMI patients receiving stents during primary percutaneous coronary intervention (PCI), who were randomized to bivalirudin vs unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor. One year after the event of stent thrombosis, patients with in-hospital (n=54) compared with out-of-hospital (n=102) stent thrombosis had significantly greater mortality (27.8% vs. 10.8%, p < 0.01); most deaths in both groups occurred within 1 week of the thrombotic event. Patients with in-hospital stent thrombosis also had higher rates of major bleeding (21.2% vs. 6.0%, p < 0.01), but a lower rate of myocardial infarction (56.6% vs. 77.5%, p < 0.01). Subacute stent thrombosis had the highest mortality. One-year mortality was significantly increased in patients with in-hospital compared with out-of-hospital ST (hazard ratio: 4.62, p < 0.01). The authors concluded that following primary PCI for STEMI, more than one-third of all stent thrombosis events during 3-year follow-up occurred during the index hospital phase. Mortality and major bleeding were significantly higher after in-hospital compared with out-of-hospital stent thrombosis (Dangas GD et al, ***J Am Coll Cardiol*** 2012;59:1752–1759).

CHARM Program: Resting Heart Rate is an Important Predictor of Outcome in Patients with Stable Chronic HF without AF, Regardless of LVEF or Beta-blocker Use

Patients enrolled in the CHARM heart failure program were divided into groups by tertiles of baseline heart rate. In the overall population, during a median follow-up of 37.7 months, 1,831 patients (24.1%) died. Individuals with a higher heart rate at baseline had a greater risk of death from any cause, compared with those with a lower heart rate (p value <0.001). A 10-beat increase in heart rate was associated with an 8% increase in the risk of death in patients without AF. Patients in the highest heart rate tertile had worse outcomes when compared with those in the lowest heart rate group. The relationship between heart rate and outcomes was similar across LVEF categories and was not influenced by beta-blocker use. However, amongst patients in AF at baseline, heart rate had no predictive value. The authors concluded that in patients with stable chronic symptomatic HF and without AF, resting heart rate is a powerful predictor of mortality and cardiovascular outcomes, irrespective of LVEF, treatment with beta-blockers, and other important prognostic factors. This easily measured clinical variable could be used in the risk stratification of these patients in everyday clinical practice (Castagno D et al, ***J Am Coll Cardiol*** 2012;59:1785–1795).

Cath PCI Registry: Antithrombotic Strategies Have Led to a 20% Reduction in Post-PCI Bleeding / Adopting the Radial Approoach & Vascular Device Closure May Further Promote this Trend

Temporal trends were examined in post-PCI bleeding from 2005 to 2009 among patients with elective PCI (n = 599,524), UA/NSTEMI (n = 836,103), and STEMI (n = 267,632). An approximate 20% reduction in post-PCI bleeding was seen (elective PCI: 1.4% to 1.1%; UA/NSTEMI: 2.3% to 1.8; STEMI: 4.9% to 4.5%). Radial approach remained low (<3%), and closure device use increased marginally from 44% to 49%. Bivalirudin use increased (17% to 30%), whereas any heparin + GPI decreased (41% to 28%). There was a significant 6% to 8% per year reduction in annual bleeding risk in UA/NSTEMI and elective PCI, but not in STEMI. Antithrombotic strategies were associated with roughly half of the reduction in annual bleeding risk: change in risk ratio from 7.5% to 4% for elective PCI, and 5.7% to 2.8% for UA/NSTEMI (both p <0.001). The authors concluded that the nearly 20% reduction in post-PCI bleeding over time was largely due to temporal changes in antithrombotic strategies, either an increase in bivalirudin use or a decrease in heparin + GPI. Changes in vascular access strategies had a smaller impact on the change in bleeding risk, likely due to the extremely low prevalence of the radial approach and a small increase in the use of vascular closure device utilization during the study. Temporal bleeding in STEMI did not change significantly (Subherwal S et al, ***J Am Coll Cardiol*** 2012;59:1861–1869).

Moderate or Severe Mitral Regurgitation in Patients Undergoing TAVI is Associated with a Higher Early, but not Late, Mortality Rate

Patients with moderate (n=89) or severe (n=43) mitral regurgitation (MR) had a higher mortality rate than those with mild or less MR (n=319) during the 30 days after transcatheter aortic valve implantation (TAVI) (hazard ratio-HR: 2.10; p = 0.02). However, the mortality rates

after 30 days were similar (HR: 0.82; p=NS). One year after TAVI, moderate MR had improved in 58%, remained moderate in 17%, and worsened to severe in 1%, and 24% of patients had died. Severe MR had improved in 49% and remained severe in 16%, and 35% of patients had died. Predictors of improved MR at 1 year were a mean transaortic gradient ≥40 mm Hg, functional MR, absence of pulmonary hypertension, and absence of atrial fibrillation. The authors concluded that moderate or severe MR in patients undergoing TAVI is associated with a higher early, but not late, mortality rate. At 1-year, MR was improved in 55% of patients with moderate or severe MR at baseline. Improvement was more likely in patients with high transaortic gradients, with functional MR, without pulmonary hypertension and without atrial fibrillation (Toggweiler S et al, ***J Am Coll Cardiol*** 2012;59:2068–2074).

ADAPT Trial: an Accelerated Diagnostic Protocol (ADP) can Successfully Identify Patients at Low Short-term Risk of a Cardiac Event and Allow Rapid Discharge from the Emergency Department

Among 1975 patients of whom 302 (15.3%) had a major cardiac event (MACE), an accelerated diagnostic protocol (ADP) which included pre-test probability scoring by the TIMI score, ECG, and 0 + 2 h values of troponin I, classified 392 patients (20%) as low risk. One (0.25%) of these patients had a MACE, giving the ADP a sensitivity of 99.7%, negative predictive value of 99.7%, specificity of 23.4%, and positive predictive value of 19.0%. Many ADP negative patients had further investigations (74.1%), and therapeutic (18.3%) or procedural (2.0%) interventions during the initial hospital stay and/or 30-day follow-up. The authors concluded that using the ADP, a large group of patients was successfully identified as at low short-term risk of a MACE and therefore suitable for rapid discharge from the emergency room with early follow-up. This approach could decrease the observation period required for some patients with chest pain (Than M et al, ***J Am Coll Cardiol*** 2012;59:2091–2098).

Post-Conditioning Reduces Infarct Size and Edema in Patients With STEMI

In 50 patients with STEMI who were randomly assigned to post-conditioning, cardiac magnetic resonance imaging was performed within 48-72 h after admission to assess myocardial edema and infarct size; the latter was also assessed by creatine kinase release. Post-conditioning, effected within 1 min of reflow after direct stenting, by balloon reinflation (4 times for 1 min with low-pressure inflations, each separated by 1 min of reflow), was associated with smaller infarct size (p = 0.01) and creatine kinase peak serum level (p = 0.003). At reperfusion, the extent of myocardial edema was significantly reduced in the post-conditioned group as compared with the control group (p = 0.03). This protective effect was confirmed after adjustment for the size of the area at risk. The authors concluded that post-conditioning reduces infarct size and edema in patients with reperfused STEMI (Thuny F et al, ***J Am Coll Cardiol*** 2012;59:2175–2181).

PRODIGY Study: Extended (24-month) Use of Dual-Antiplatelet Therapy is not More Effective than a 6-Month Duration of Clopidogrel Followed by Aspirin Monotherapy

A total of 2013 patients were randomly assigned to receive bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent implantation. At 30 days, patients were randomized to receive up to 6 or 24 months of clopidogrel therapy in addition to aspirin. The primary end point was a composite of death of any cause, myocardial infarction, or cerebrovascular accident. The cumulative risk of the primary outcome at 2 years was 10.1% with 24-month dual-antiplatelet therapy compared with 10.0% with 6-month dual-antiplatelet therapy (hazard ratio, 0.98; *P*=NS). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between the study groups; however, there was a consistently greater risk of hemorrhage in the 24-month clopidogrel group. The authors concluded that a regimen of 24 months of clopidogrel therapy in patients who receiving a mixture of drug-eluting or bare-metal stents was not significantly more effective than a 6-month clopidogrel regimen in reducing the composite of death due to any cause, myocardial infarction, or cerebrovascular accident. (Valgimigli M et al, ***Circulation*** 2012;125:2015-2026).

Low Incidence of SCD and Low Risk of Supraventricular Tachycardia in Asymptomatic Patients with Wolff-Parkinson-White ECG Pattern

A total of 20 studies reporting on 1869 asymptomatic patients with preexcitation who did not undergo ablation were included in this metaanalysis. Participants were primarily male (mean age 7 - 43 years). Ten SCDs were reported at follow-up. Seven studies originated from Italy and reported 9 SCDs. The risk of SCD is estimated at 1.25 per 1000 person-years. A total of 156 supraventricular tachycardias were reported involving 9884 person-years from 18 studies. The risk of supraventricular tachycardia was 16 events per 1000 person-years of follow-up. Children had a bit higher SCD

(1.93 vs 0.86; *P*=0.07) and supraventricular tachycardia (20 vs 14; *P*=NS) event rates compared with adults. The authors of this metaanalysis concluded that there is a low incidence of life-threatening arrhythmia in patients with asymptomatic preexcitation, which argues against routine invasive management in most asymptomatic patients with the WPW ECG pattern (Obeyesekere MN et al, ***Circulation*** 2012;125:2308-2315).

Electronic Control Devices (ECD) (TASER X26) Can Cause Cardiac Arrest

The author studied 8 cases of loss of consciousness induced by an electronic control device (ECD), TASER X26. First recorded rhythms were ventricular tachycardia/ fibrillation in 6 cases and asystole (after ~30 minutes of nonresponsiveness) in 1 case. An external defibrillator reported a shockable rhythm in 1 case, but no recording was made. This report offers evidence detailing the mechanism by which an ECD can produce transthoracic stimulation resulting in cardiac electrical capture and ventricular arrhythmias leading to cardiac arrest (Zipes DP, ***Circulation*** 2012;125:2417-2422).

ACUITY Trial: Incomplete revascularization after PCI in Patients with Acute Coronary Syndromes is Strongly Associated with 1-year MI, Repeat Revascularization, and Major Cardiac Events

Quantitative angiography was performed in 2954 patients with acute coronary syndromes. With use of diameter stenosis cutoffs ≥30%, ≥40%, ≥50%, ≥60%, and ≥70%, the prevalence of incomplete coronary revascularization (ICR) after PCI was 75%, 55%, 37%, 25%, and 17%, respectively. The 1-year major adverse cardiac event (MACE) rate was increased among patients with ICR. ICR was associated with higher 1-year rates of MI (12.0% vs 8.2%; hazard ratio-HR, 1.50; *P*=0.0007) and ischemia-driven unplanned revascularization (15.7% vs 10.2%; HR, 1.58; *P*<0.0001), with a trend toward increased mortality (3.1% vs 2.2%; HR, 1.43; *P*=0.13). By multivariable analysis, ICR was an independent predictor of 1-year MACE (HR, 1.36; *P*=0.002). The impact of ICR on MACE was similar regardless of chronic total occlusion presence, but it was more pronounced with a greater number of nonrevascularized lesions. The authors concluded that ICR was strongly associated with 1-year myocardial infarction, ischemia-driven unplanned revascularization, and MACE (Rosner GF et al, **(*Circulation*.** 2012;125:2613-2620).

ISSUE-3 Trial: 15% of Patients with Severe Asystolic Neurally Mediated Syncope Fulfilled the Criteria for a Pacemaker which Reduced Recurrences by 57%

Initially, 511 patients, ≥40 years, who had experienced ≥3 syncopal episodes in the previous 2 years, received an implantable loop recorder (ILR); 89 of these had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope and met criteria for pacemaker implantation; 77 of 89 patients were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. Syncope recurred in 27 patients, 19 of whom had been assigned to pacemaker OFF and 8 to pacemaker ON. The 2-year estimated syncope recurrence rate was 57% with pacemaker OFF and 25% with pacemaker ON (1P=0.039). The risk of recurrence was reduced by 57%. Complications occurred in 5 patients: lead dislodgment (n=4) and subclavian vein thrombosis (n=1). The authors concluded that dual-chamber permanent pacing is effective in reducing (by 57%) recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope (Brignole M et al, ***Circulation*** 2012;125:2566-2571).

ROOBY Trial: Off-Pump CABG is Associated With Worse Arterial and Saphenous Vein Graft Patency and Less Effective Revascularization

A total of 2203 patients were randomized to off-pump vs on-pump coronary bypass (CABG) (2/2002-5/2007). Follow-up angiograms were obtained in 685 off-pump (62%) and 685 on-pump (62%) patients and were analyzed for FitzGibbon classification (A=widely patent, B=flow limited, O=occluded) and effective revascularization (all 3 diseased major coronaries with significant disease revascularized by FitzGibbon A-quality, with no new postanastomotic lesions). Off-pump CABG resulted in lower FitzGibbon A patency rates than on-pump CABG for arterial conduits (85.8% vs 91.4%; *P*=0.003) and saphenous vein grafts (72.7% vs 80.4%; *P*<0.001). Fewer off-pump patients were effectively revascularized (50.1% vs 63.9% on-pump; *P*<0.001). The 1-year adverse cardiac event rate was 16.4% in patients with ineffective revascularization vs 5.9% in patients with effective revascularization (*P*<0.001). The authors concluded that off-pump CABG resulted in significantly lower FitzGibbon A graft patency and less effective revascularization than on-pump CABG. At 1 year, patients with less effective revascularization had higher adverse event rates (Hattler B et al, ***Circulation*** 2012;125:2827-2835).

Drug Eluting Stents (DES) are Highly Efficacious at Reducing Short- and Long-Term Risk of Target Vessel Revascularization without an Increase in any Safety Outcomes, Including Stent Thrombosis, Compared with BMS

Analysis of 76 trials enrolling 57,138 patients showed that compared with bare metal stents (BMS), each drug-eluting stent (DES) reduced long-term target-vessel revascularization (39%–61%), but the magnitude varied by DES type (everolimus eluting-EES~sirolimus eluting-SES~zotarolimus eluting Resolute-ZES-R>paclitaxel eluting-PES~ZES>BMS), with a >42% probability that EES had the lowest target-vessel revascularization rate. There was no increase in the risk of any long-term safety outcomes, including stent thrombosis, with any DES (vs BMS). There was also reduction in MI (all DES except PES vs BMS) and stent thrombosis (with EES vs BMS). The safest DES appeared to be EES (>86% probability), with reduction in MI and stent thrombosis compared with BMS. Short-term outcomes were similar to long-term outcomes, with SES, ZES-R, and EES being the most efficacious and EES being the safest stent. The authors concluded that DES are highly efficacious at reducing the risk of target-vessel revascularization without an increase in any safety outcomes, including stent thrombosis, compared with BMS. However, among the DES types, there were considerable differences, such that EES, SES, and ZES-R were the most effective and EES was the safest stent in terms of stent thrombosis **(**Bangalore S et al, ***Circulation*** 2012;125:2873-2891).

PLATO Trial: Treatment with Ticagrelor should not be Withheld in Acute Coronary Syndrome Patients with a History of Ischemic Stroke or TIA for Safety Concerns if Otherwise Indicated

Treatment effects of ticagrelor vs clopidogrel were evaluated n patients with acute coronary syndrome with and without a history of prior stroke or TIA in the PLATO trial. Of the 18,624 randomized patients, 1152 (6.2%) had a history of stroke or TIA. Such patients had higher rates of MI (11.5% vs 6.0%), death (10.5% vs 4.9%), stroke (3.4% vs 1.2%), and intracranial bleeding (0.8% vs 0.2%) than patients without prior stroke or TIA. However, the reduction of the primary composite outcome and total mortality at 1 year with ticagrelor vs clopidogrel was consistent with the overall trial results: 19.0% vs 20.8% (hazard ratio-HR, 0.87; *P*=NS) and 7.9% vs 13.0% (HR, 0.62). The overall PLATO-defined bleeding rates were similar: 14.6% vs 14.9% (HR, 0.99), and intracranial bleeding occurred only in 4 cases in each group. The authors concluded that patients with acute coronary syndrome with a prior history of ischemic stroke or TIA had higher rates of clinical outcomes than patients without prior stroke or TIA. However, the efficacy and bleeding results of ticagrelor in these high-risk patients were consistent with the overall trial population, with a favorable clinical net benefit (James SK et al, ***Circulation*** 2012;125:2914-2921).

Early Surgery in Patients With Infective Endocarditis and Large Vegetations Significantly Reduced Mortality and Embolic Events

Patients with left-sided infective endocarditis, severe valve disease, and large vegetations were randomized to early (within 48 h) surgery (n=37) or conventional treatment (n=39); with 30 patients (77%) of the latter group finally having surgery during initial hospitalization (n=27) or during follow-up (n=3). The primary end point (in-hospital death and embolic events) occurred in 1 patient (3%) in the earlysurgery group as compared with 9 (23%) in the conventional-treatment group (hazard ratio-HR, 0.10; P = 0.03). The rate of the composite end point of death from any cause, embolic events, or recurrence of infective endocarditis at 6 months was 3% in the early-surgery group and 28% in the conventional-treatment group (HR, 0.08; P = 0.02). The authors concluded that early surgery in patients with infective endocarditis and large vegetations significantly reduced the composite end point of death from any cause and embolic events (Kang D et al, ***N Engl J Med*** 2012;366:2466-2473).

Important Review and Other Articles

New oral anticoagulants in AF & ACS (De Caterina R et al, ***J Am Coll Cardiol*** 2012; 59:1413-1425), PFO (Kutty S et al, ***J Am Coll Cardiol*** 2012;59:1665-1671), Ventricular arrhythmias in normal heart (Prystowsky EN et al, ***J Am Coll Cardiol*** 2012;59:1733-1744), Appropriateness of coronary revascularization for patients without ACS (Hannan EL et al, ***J Am Coll Cardiol*** 2012;59:1870-1876), 2012 Appropriate use criteria for diagnostic catheterization (Patel MR et al, ***J Am Coll Cardiol*** 2012;59:1-33), Expert consensus statement for TAVI (Tommaso CL et al, ***J Am Coll Cardiol*** 2012;59:2028-2042), Sudden cardiac death and genetic ion channelopathies (Napolitano C et al, ***Circulation*** 2012;125:2027-2034), Sudden cardiac death in the athlete (Link & Estes, ***Circulation*** 2012;125:2512-2516), Thrombolytic therapy of acute stroke **(**Feske SK, ***Circulation*** 2012;125:2662-2666)**,** Antithrombotic therapy in patients with chronic kidney disease (Capodanno & Angiolillo, ***Circulation*** 2012;125:2649-2661), Bleeding and thrombosis in patients with continuous-flow ventricular assist devices **(**Eckman & John, ***Circulation*** 2012;125:3038-3047), Genetics & cardiovascular disease (Ashley EA et al, ***Circulation*** 2012;126:142-157), VT ablation (Wissner E et al, ***Eur Heart J*** 2012; 33:1440-1450).