

Um congresso para recordar

FAUSTO J. PINTO

fpinto@icvl.pt

Editor da RPC

Rev Port Cardiol 2009; 28 (11): 1309-1344

O Congresso da ESC (European Society of Cardiology), presentemente o maior no Mundo na área Cardiovascular, foi este ano organizado em Barcelona de 29 de Agosto a 2 de Setembro de 2009. Entre outros aspectos a assinalar é com muito orgulho que posso afirmar que Barcelona 2009 ficará na história da Cardiologia Portuguesa como aquele em que a participação nacional teve maior notoriedade e impacto. Para além da figura do Presidente do Congress Program Committee (CPC), que tive a honra de desempenhar, mais dois colegas participaram nos trabalhos do CPC, o Dr. Miguel Mendes como membro efectivo do CPC e o Dr. Miguel Sousa Uva, como *chairman* do *working group* de cirurgia cardíaca. O Prof Lino Gonçalves foi *chairman* do *Webcast committee*, responsável por um dos sucessos da veiculação do Congresso através deste meio de comunicação.

Pela primeira vez foram atingidos vários recordes no que respeita à participação efectiva da Cardiologia portuguesa. Assim, no âmbito do programa científico foram convidados 36 colegas como moderadores e/ou palestrantes, que desempenharam 60 tarefas diferentes. Em anos anteriores o máximo de participação tinha sido de 11 colegas. Este ano foi também um ano *record* no número total de abstracts submetidos para o Congresso, com um total de 9848, dos quais 4085 foram aceites. Portugal ficou pela primeira vez em 10º lugar no número de abstracts submetidos (308) e 11º no número de aceites (102). Tal

representa, sem dúvida, a expressão do crescimento e maturidade da cardiologia científica portuguesa a que não é alheio o esforço realizado pelos diferentes centros nacionais na procura da excelência. Claro que este é um trabalho contínuo, não nos devendo deslumbrar com os bons resultados, mas continuando a trabalhar no sentido de melhorar ainda mais tudo aquilo que tem sido conseguido, uma vez que muito há ainda a fazer. Este Congresso também é o reconhecimento por parte da comunidade internacional do papel desempenhado por alguns dos mais prestigiados membros da Cardiologia portuguesa, que ao longo dos anos e desde o início da sua fundação, têm procurado elevar o nome de Portugal. Nunca será demais realçar a importância para a nossa cardiologia do reforço da presença de membros nacionais nos mais variados órgãos internacionais. Cabe à Sociedade Portuguesa de Cardiologia e à sua liderança a responsabilidade de continuar a apostar fortemente no apoio a esse desígnio pois tal representará, sem dúvida, um valor acrescido de inquestionável benefício para a Cardiologia Portuguesa.

Neste número publicamos dois documentos importantes: O resumo das *Highlights* do Congresso, onde se condensaram os aspectos mais relevantes que aconteceram ao longo dos dias; os abstracts dos principais ensaios clínicos que foram apresentados em Barcelona.

Até ao Estocolmo 2010.

HIGHLIGHT SESSION AT ESC 2009

The Highlight Session of ESC Congress was presented by nine top European experts that had the difficult task of summarizing the more relevant presentations occurring during the whole Congress:

Prof Barbara Casadei from Oxford, UK, presented the Basic Science. She considered three main areas: 1. Genetic component of cardiovascular disease, particularly in coronary artery disease, including the identification of new loci affecting risk and the identification of new targets. She also alluded to epigenetics, defined as interactions between genes with their environment which bring the phenotype into being, and showed a study underlying the interaction of high fat diet with genotype to affect molecular phenotype; 2. Atrial fibrillation risk assessment, including a study of genome-wide association where a sequence variant in the ZFHX3 gene on chromosome 16p22 confers risk of both common AF and ischemic stroke in populations of European descent; 3. Oxidative signalling, including several studies on oxidative stress in the fibrillating human atrium, as a marker of visceral fat accumulation, related to adiponectin synthesis from perivascular adipose tissue in human atherosclerosis and reduced by chronic inhibition of rac-1 GTPase leading to improvement of endothelial function and attenuation of atherosclerotic plaque development.

Prof Robert Fagard from Leuven, Belgium, presented Hypertensions and Risk Factors. He discussed the following topics: 1. Blood pressure measurement and prognosis, where he quoted the Malmo Prevention Project where orthostatic hypotension was identified as a risk marker for mortality and coronary events, and the PAMELA study on ambulatory blood pressure measurement, where the Morning blood pressure surge was not shown to be an independent predictor of cardiovascular risk; 2. Management of hypertension, including pharmacological, where the HYVET trial has shown benefit from antihypertensive treatment in octogenarians and non-pharmacological,

such as dietary manipulations of Na, K, Mg and Ca, moderate alcohol intake, which decreases the risk of CAD and total mortality (wine appears to be somewhat superior to beer with regard to the reduction of vascular disease risk), fish oil and low, moderate or high intensity exercise; 3. What's new in the ESC/ESH 2007 guidelines? Some aspects were highlighted during the meeting such as the importance of global cardiovascular risk assessment, adding a drug from another class is more effective than doubling the dose of the same drug, initiation with combination treatment is associated with earlier BP control, better tolerability and compliance, the BP level below which vital organ perfusion is impaired is likely to differ according to patient characteristics, for instance, post-hoc analyses of trials suggest that in high CV risk patients there is some reason for concern below 120/75 mmHg.

Prof Frank Rademakers from Leuven, Belgium, presented Imaging. He divided his presentation in: 1. Diagnosis, where he showed one animal study demonstrating fibrosis as the culprit for arrhythmias in a pre-clinical stage of myocardial disease by T2 fibrosis quantification; and another one using FDG-PET/CT showing that peri coronary inflammation contributes to progression and instability of the atherosclerotic plaque; in another study using CMR was shown that false positive perfusion abnormalities can be due to spasm or microvascular dysfunction. The CMR Registry of over 11 000 patients showed an impact on patient management, such as new diagnosis and/or therapeutic consequences in 62% of the patients. 2. Prognosis. Tissue Doppler parameters of fibrillatory wall predict recurrence; by PET stress perfusion adds to rest imaging and provides 3yr "warranty"; in the setting of acute MI the % salvaged myocardium assessed by T2 is strong predictor of MACE and remodelling. In a 5 year follow up study using 2D and 3D Echocardiography, 3D outperforms 2D as management tool for

therapeutic decisions and in another prognostic study global longitudinal strain was better than EF or WMS for assessment of global function and prognosis. In a stress echo involving 5355 patients the pattern of ischemia and RWMA carries different prognostic information in normals versus hypertensives. 3. Technique. The use of molecular imaging to assess myocardial ischemic memory, transplant rejection, atherosclerosis and angiogenesis is promising and other new technologies such as vorticity imaging are still at very early stages of development.

Professor Panos Vardas from Crete, Greece, presented Arrhythmias. The main areas included were: 1. Mechanisms. Two studies were presented, one showing left atrial high density mapping during sinus rhythm, coronary sinus pacing and atrial fibrillation: evidence of rhythm-dependent (functional) fractionation; and another showing that AF leads to electrical remodelling of Na currents, highlighting the role of INa inhibition by Ranolazine on arrhythmias and contractility.

2. Genetics. The role of genetic testing in risk stratification of Brugada syndrome based on a study that showed that the presence of a mutation leading to a truncated protein is associated with more than a 3-fold increase in the risk of sudden cardiac death or ventricular fibrillation in Brugada SCN5A mutation carriers.

3. New techniques: Diagnostic and therapeutic. Implantable loop recorders for syncope, including the REVISE study, the first prospective study to show, by means of ILR, a high incidence of asystole in patients misdiagnosed with epilepsy, or where the diagnosis of epilepsy was in doubt; Remote monitoring of ICD patients; Remote magnetic navigation for AF ablation

4. Registries and Clinical Outcomes. Results from the FINGER Brugada Registry on long term prognosis of patients diagnosed with Brugada syndrome was presented, showing that the cardiac event rate per year was 7.7% in patients with a history of aborted SCD, 1.9% in patients with syncope and only 0.5% in asymptomatic individuals. Significantly impro-

ved left ventricular ejection fraction after AF ablation, in patients with heart failure and impaired LV contractility. Incidence of mortality and appropriate shocks in patients with ischemic and non-ischemic cardiomyopathy after receiving ICDs, showing the prevalence of appropriate shocks was similar in patients with ischemic and non-ischemic cardiomyopathy

5. Clinical Trials. The MADIT-CRT trial which showed 34% reduction in death or HF in minimally symptomatic patients with ischemic or non-ischemic cardiomyopathy; 41% reduction in HF events and improvement in LV function; more effective in women than in men and in patients with wider rather than narrow QRS complexes; prevents HF in minimally symptomatic at risk cardiac patients.

REVERSE Trial European Cohort: 24 Months Follow Up. CRT in NYHA I and II HF patients on optimal medical therapy improves clinical outcome, ventricular structure and function and thus modifies disease progression with a more pronounced effect in NYHA II patients; QRS width is an independent and strong predictor of reverse remodeling, indicating that electrical dyssynchrony is important for the response to CRT in mild HF.

RELY trial where Dabigatran 150 mg twice daily, significantly reduced stroke compared to warfarin with similar risk of major bleeding; Dabigatran 110 mg twice daily, had a similar rate of stroke as warfarin with significantly reduced major bleeding; both doses markedly reduced intra-cerebral, life-threatening and total bleeding and Dabigatran had no major toxicity, but did increase dyspepsia and GI bleeding.

6. Guidelines for the diagnosis and management of syncope. The main messages were: A new diagnostic approach is proposed, focusing on risk stratification for sudden cardiac death, for the patient with an uncertain diagnosis on initial evaluation of a syncopal episode and emphasis and priority are given to a diagnostic strategy based on prolonged ECG monitoring (i.e. wearable/im-

plantable loop recorders) in contrast to the conventional strategy based on laboratory testing (i.e. tilt testing, ∂P studies).

Professor Keith Fox resented the highlights on Acute Coronary Syndromes. He alluded to some of the clinical trials presented at the meeting related to the pharmacological treatment of ACS. The first question relates to the use of standard or double dose of clopidogrel. CURRENT OASIS 7 looked at this problem and the main conclusions were: Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (composite of CV death, MI or stroke) in PCI; in patients not undergoing PCI, double dose clopidogrel was not significantly different from standard dose (70% had no significant CAD or stopped study drug early for CABG); there was a modest excess in CURRENT-defined major bleeds but no difference in TIMI major bleeds, ICH, fatal bleeds or CABG-related bleeds. The second regards the use of more potent P2Y12 antagonists: risk vs benefit? The PLATO trial showed superiority of a new oral reversible P2Y12 antagonist, ticagrelor, compared with clopidogrel, regarding less MACE and stent thrombosis. The absence of significant influence of proton pump inhibitors shown in several trials was also referred.

Professor Carlo di Mario from London, UK, presented Interventional Cardiology. He started with the polemic on Drug Eluting Stents quoting the SCAARS study which showed no difference between bare metal and drug eluting stents for death and MI. To the question: Is it time to turn the page? He replied: Yes, because we have learned from history that: Long term follow-up of large registries indicate a similar or lower mortality and MI risk for DES vs. BMS (on- and off label); also in high risk patients such as STEMI and diabetes long term follow-up of large registries are reassuring and late stent thrombosis is rare but seems uniquely associated with DES. The Spanish ESTROFA Registry also showed no significant difference in stent thrombosis between three different second generation DES. The ISAR-TEST 4 study showed no difference in outcome between

biodegradable and permanent polymers. New imaging methods, such as OCT may help understand the mechanisms of late wall coverage after DES. TRYTON-TIMI 38 showed no significant effects of proton pump inhibitors either with clopidogrel or prasugrel. The SYNTAX trial update at 2 years follow up showed no significant difference between CABG vs PCI for all cause death/CVA or MI, however a higher repeat revascularization was seen in the PCI group (17.4% vs 8.6%). The use of fractional flow reserve for detection of hemodynamically significant lesions was assessed on the FAME study that had an update of the 18 months follow up presented at this meeting, continuing to show a better outcome on the FFR-guided group. The TRIANA study on Primary Angioplasty versus Fibrinolysis in the Very Elderly showed that in this older population the use of primary PCI was superior to thrombolysis. Finally the NORDISTEMI study revealed that an early invasive strategy is superior to the conservative approach in a group of patients with delayed PCI access superior to 90 minutes.

Dr Rosenheck from Vienna presented the valvular heart disease. He started to show a study demonstrating that HDL may attenuate inflammation and inhibit calcification of aortic valves. In another study in rabbits Atorvastatin Attenuates Severe Myxomatous Mitral Regurgitation via Lrp5/Sox9 Pathways. In another study was shown an increased Afterload and Impaired Intrinsic Ventricular Function in a group of patients with Paradoxical Low Flow Aortic Stenosis. In another study in patients with severe aortic stenosis, a low mean gradient is associated with: Lower longitudinal myocardial function; higher degree of interstitial / subendocardial Fibrosis and poor long term outcome. The use of CT for aortic stenosis quantification was referred. The use of a risk score to stratify patients with moderate and severe aortic stenosis including peak velocity and BNP was shown. Another study assessed risk stratification by consideration of ventricular, vascular and valvular components of the disease, including: Peak aortic jet velocity, Valvulo-arterial

impedance, longitudinal strain, indexed LA area. The Impact of Functional Mitral Regurgitation after Myocardial Infarction and its contribution to LV enlargement and outcome was shown. The use of echo to assess the ascending aorta was compared with CT. The management strategy for transcatheter AVI was shown. The main changes introduced by new guidelines on endocarditis were summarized in the following: The principle of antibiotic prophylaxis when performing procedures at risk of IE in patients with predisposing cardiac conditions is maintained, but Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures; Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE; Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE; Whether the reduced use of prophylaxis is associated with a change in the incidence of IE must be evaluated by prospective studies.

Professor Marco Metra from Italy presented Heart Failure. He referred to: Prognostic factors-LVEF and Red blood cells Distribution Width; Prevention of symptomatic HF-Heart rate, Diabetes, Atrial fibrillation, Wide QRS; Treatment of HF-Beta-blocking agents, Inotropic agents, Diuretics/ renal protection and Devices. The MAGGIC meta analysis in over 43 000 patients showed a better survival in patients with heart failure and preserved EF compared with the ones with low EF. The RECORD study showed that rosiglitazone increases the risk of HF by approximately 2 fold compared with control; more deaths due to HF were observed in the rosiglitazone group (10 vs. 2), but overall no increase in CV or all-cause mortality was observed; duration of HF admissions and rehospitalisation for HF after 1st HF event was similar in both groups; overall, these findings support the current recommendation that rosiglitazone should not be used in patients with symptomatic HF and should not continue to be used in the presence of HF. The MADIT-CRT trial was also

referred. The B-Convinced trial showed that keeping beta blockers in HF patients had no effect in dyspnea symptoms and outcome. The HFA/EHRA ESC CRT survey: Pre-implantation Data was also mentioned.

Professor J Perk from Stockholm showed the highlights of the highlight of the Congress, Prevention. He started with observational studies: Trends in resting heart rate from 1991 to 2007 were studied in 332.578 French Adults: Heart rate decreased in unselected population in both men (5 bpm) and women (7 bpm) in the first decade but remained stable thereafter. In the Copenhagen city heart study resting heart rate remains a risk factor. In another study the levels of fibrinogen and HS-CRP increased with rising RHR: relative risk for CV mortality per 10 bpm increase: 1.2 for CV mortality adjusted for conventional risk factors. The presence of increased hair cortisol levels in patients with acute myocardial infarction underlines the role of stress and lifestyle in AMI patients. In another study, right atrial enlargement, P-wave extension, PR and QTc intervals prolonged were observed after acute red wine consumption. Followed with Explanation studies: In the dilator study was studied the Impact of smoking prohibition in bars, restaurants and discotheques on employees endothelial function. It showed that after application of the law FMD normalised in the exposed group. The law contributes to a protection of workers against the risk of cardiovascular damage. Another study looked at the Effects of endurance training on telomere length and senescence of circulating cells in professional athletes and matched controls without physical exercise.

The authors showed that long-term continuous exercising induces a potent inhibition of the leukocyte telomere erosion observed in sedentary individuals. A study looking at generalized vascular damage and impaired endogenous regenerative capacity in children with obesity showed that already in early childhood, obesity is associated with pronounced metabolic alterations and an impaired endogenous regenerative capacity. A

set of translational studies showed: Intensive exercise training leads to improved endothelial function in school children; a consultation-based method is equal to SCORE and an extensive laboratory-based method in predicting risk of future cardiovascular disease. Some application studies that were presented: Prevalence of lipid disorders in statin treated patients from Sweden, Norway and Denmark: Results from the Dyslipidemia International Study (DYSIS) showed significant improvements in lifestyle, weight management and aerobic fitness in coronary patients, HRI and their partners; Cardiovascular prevention is not only for cardiologists, the example of the city of Ferrara. Transforming an entire city towards heart-healthy behaviour by Surveillance, Prevention and Assessment, engaging all layers of society, including decision makers,

education and industry. As from 2010 one hour of daily education on national TV. In the prevention perspective two interesting studies: One looking at mercury rising related with global warming, carbon and cardiovascular health. There is a correlation between intake of red meat and CVD. Recommend < 500 gr red meat weekly to lower risk of CVD and contribute to attenuating global warming. Cars, fumes and cardiovascular disease. In fact, small particles pass alveolar wall, transport by LDL to vascular wall, therefore influencing on vascular wall inflammation. Small but significant increased risk at population level with potential relevance demonstrated by the special map of London and initiatives in Canada. Finally showed a study that revealed lack of association between watching football matches and risk of acute cardiovascular events.

Hotlines and Clinical Trial Uptades (CTUs)

Randomised controlled trial of low dose aspirin in the prevention of cardiovascular events and death in subjects with asymptomatic atherosclerosis

Topics: Cardiovascular Disease Prevention - Risk Assessment and Management

Session number: 175-176

Session title: Randomised controlled trial of low dose aspirin in the prevention of cardiovascular events and death in subjects with asymptomatic atherosclerosis

Authors: Fowkes, Gerry - Patrono, Carlo



Presenter | see Discussant report
Gerry Fowkes
(United Kingdom)

List of Authors:

FGR Fowkes, JF Price, MCW Stewart, I Butcher, GC Leng, ACH Pell, PAG Sandercock, KAA Fox, GDO Lowe, GD Murray for the Aspirin for Asymptomatic Atherosclerosis trialists, University of Edinburgh

Abstract:

The effectiveness of antiplatelet therapy in preventing major vascular events in patients with known cardiovascular disease is well established but the value of antiplatelets in primary prevention remains unclear. The ankle brachial index (ABI) which is the ratio of systolic pressure at the ankle to that in the arm is an indicator of subclinical atherosclerosis and has been shown convincingly in many cohort studies of healthy populations to predict the risk of major vascular events independently of established cardiovascular risk factors. Thus individuals free of clinical cardiovascular disease but with a low ABI may be a high risk group which could benefit from antiplatelet therapy in a similar way to those with established clinical disease. Since the ABI is a simple, inexpensive, non-invasive test, it has the potential to be used in cardiovascular screening programmes but whether those with a low ABI should be prescribed antiplatelets such as aspirin is unknown. From April 1998 to December 2001, 28,980 men and women aged 50 to 80 years and free of cardiovascular disease were recruited from GP age sex registers in Lanarkshire, Glasgow and Edinburgh in Scotland and had an ABI screening test. 3350 with a low ABI (≤ 0.95) were entered into the trial and randomised to 100mg

enteric coated aspirin or matching placebo. The sample size of 3350 gave 80% power at 5% significance level (2 sided) to detect a reduction in the proportion of patients with at least one primary endpoint from 12% on placebo to 9% on aspirin. Subjects entered into the trial had a clinic follow up visit at 3 months and 1 year. Subsequent follow up for a mean of 8.2 years was annually by telephone with an intervening 6 monthly letter. Contact has been maintained with 95% of survivors. At 5 years, 2557 subjects (85% of survivors) had a detailed clinical follow up examination. Cardiovascular events and deaths have also been ascertained by flagging of GP notes, review of hospital discharges in Scotland using record linkage, and flagging of deaths at NHS Central Registry. The Outcome Events Committee provided confirmation of events by review of medical records and death certificates.

The primary endpoint was a composite of initial fatal or nonfatal coronary event or stroke or revascularisation. The two secondary endpoints were (1) all initial vascular events defined as a composite of a primary endpoint event or angina, intermittent claudication or transient ischaemic attack; and (2) all cause mortality. A total of 357 participants had a primary endpoint event (13.5 per 1000 person years, 95%CI 12.2 to 15.0). No statistically significant difference was found between those allocated to aspirin or placebo (181 v 176 events) (hazard ratio [HR] 1.03, 95% CI 0.84 to 1.27). A vascular event comprising the secondary endpoint occurred in 578 participants (22.8 per 1000 person years, 95% CI 21.0 to 24.8) and no statistically significant difference was found between the aspirin and placebo groups (288 v 290 events) (HR 1.00, 95% CI 0.85 to 1.17). All cause mortality was similar in both groups (176 v 186 deaths) (HR 0.95 95% CI 0.77 to 1.16). An initial event of major haemorrhage requiring admission to hospital occurred in 34 (2%) of participants in the aspirin group and 20 (1.2%) in the placebo group. (HR 1.71, 95% CI 0.99 to 2.97).

These findings do not support the routine use of aspirin for the prevention of vascular events in the context of ABI screening in the general population.



Discussant see Presenter report
Carlo Patrono,
FESC (Italy)

Report:

A low ankle brachial index (ABI) indicates peripheral atherosclerosis in the legs and an increased risk of cardiovascular and cerebrovascular events. Some guidelines recommend antiplatelet prophylaxis for asymptomatic individuals with a low ABI, in the absence of direct trial evidence. The aim of the AAA trial was to determine the efficacy and safety of low-dose aspirin in preventing major vascular events in subjects with no history of vascular disease but with asymptomatic atherosclerosis as indicated by an ABI 0.95.

The primary end-point of the study was a composite of initial fatal or non fatal coronary event or stroke or revascularization. The trial was powered to detect a 25% proportional risk reduction in major vascular events. After ABI screening, 3350 men and women (about 70%) aged 50 to 75 years (mean age, 62 yr) were allocated randomly to enteric coated aspirin 100 mg once daily or placebo. The mean duration of follow-up was 8.2 years. Overall, participants were assessed as compliant with the study medication for 60% of participant years of follow-up. A total of 357 subjects had one or more validated primary endpoint events, resulting in an incidence of 1.4 per 100 person years. No statistically significant difference was found between the aspirin and placebo groups (181 vs 176 events, HR 1.03, 95%CI 0.84 to 1.27). All cause mortality was similar in both groups. An initial event of major bleeding requiring hospital admission occurred in 34 (2%) of participants in the aspirin group and 20 (1.2%) in the placebo group (HR 1.71, 95%CI 0.99 to 2.97). How are these apparently negative findings to be interpreted in the light of the recent Antithrombotic Trialists' (ATT) collaborative meta-analysis of aspirin trials? In the 6 primary prevention trials among 95000 individuals at low average risk, aspirin allocation yielded a 12% proportional reduction in serious vascular events, due mainly to a reduction of about a fifth in non fatal myocardial infarction. The net effect on stroke was not significant and vascular mortality did not differ significantly. Aspirin allocation increased major gastrointestinal and extracranial bleeds by about 50%. If the true effect of aspirin in people with asymptomatic atherosclerosis was a 12% reduction in risk (as in the ATT meta-analysis), then the sample size of the AAA trial would have had to be about 4 times larger to achieve the intended statistical power. For each outcome, there was substantial overlap between the AAA and ATT primary prevention results, so lack of power (amplified by relatively poor compliance) does seem to provide a reasonable explanation for the AAA null findings. In fact, an updated meta-analysis that includes the major vascular events from the AAA trial does not indicate any definite evidence of heterogeneity between the AAA and the other 6 trials for any single endpoint (ATT Collaboration, unpublished). Other explanations may help interpreting the AAA results. Thus, it has been suggested that the presence of peripheral arterial disease (PAD), whether symptomatic or asymptomatic, may render platelet activation more critically dependent on ADP than TXA2 release. Moreover, accelerated platelet turn-over associated with PAD may be responsible for faster renewal of unacetylated platelet COX-1, thereby blunting the antiplatelet effect of low-dose aspirin given once daily. Until additional information is available, perhaps the most reliable estimate of aspirin effects on particular vascular outcomes in people with asymptomatic atherosclerosis may be derived from the updated ATT meta-analysis.

Comparison of Ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: results of the PLATElet inhibition and patient Outcomes (PLATO) trial

Topics: Acute Coronary Syndromes (ACS)

Session number: 179-180

Session title: Comparison of Ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: results of the PLATElet inhibition and patient Outcomes (PLATO) trial

Authors: Wallentin, Lars - Kristensen, Steen Dalby



Presenter | see Discussant report
Lars Wallentin, FESC (Sweden)

List of Authors:

Lars Wallentin, Richard C. Becker, Andrzej Budaj, Christopher P Cannon, Håkan Emanuelsson, Claes Held, Jay Horrow, Steen Husted, Stefan James, Hugo Katus, Kenneth M Mahaffey, Benjamin M Scirica, Allan Skene, Philippe Gabriel Steg, Robert F. Storey, and Robert A. Harrington for the PLATO investigators.

Abstract:

Ticagrelor versus clopidogrel in patients with acute coronary syndromes: the PLATElet inhibition and patient Outcomes (PLATO) trial. Current clinical practice guidelines for patients with acute coronary syndrome recommend dual antiplatelet treatment with aspirin and clopidogrel. The efficacy of clopidogrel is hampered by slow and variable transformation of the prodrug to the active metabolite, modest and variable platelet inhibition, increased risk of bleeding and increased risk of stent thrombosis and myocardial infarction in poor responders. Ticagrelor is an oral reversible direct acting P2Y12-inhibitor providing a faster and larger platelet inhibition than clopidogrel. The PLATO trial was a multicenter double-blind randomized trial, comparing treatment with ticagrelor (180 mg loading dose followed by 90 mg twice daily) to treatment with clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) for prevention of cardiovascular events. We included 18,624 patients admitted either with ST-elevation ACS intended for primary PCI (38%) or with non-ST-elevation ACS intended for an invasive or medical approach (62%). Prior to randomization 94% were treated with aspirin; 46% with clopidogrel. The patients were treated for an average of 278 days (minimum 6 and maximum 12 months). The follow-up was complete in 99.97% with only 5 patients lost to follow-

up. The primary composite of death from vascular causes (CV) death, myocardial infarction (MI) and stroke was reduced from 11.7% to 9.8% (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; $P < 0.001$). In the predefined hierarchical testing of secondary endpoints there were reductions of the composites of total death, MI and stroke from 12.3% to 10.2% ($P = 0.0001$), CV-death, MI, stroke, severe recurrent, recurrent ischemia, transient ischemic attack (TIA) and other arterial thrombotic events from 16.7% to 14.6% ($P < 0.001$), MI alone from 6.9% to 5.8% ($P = 0.005$) and CV-death from 5.1% to 4.0% ($P = 0.001$). Total mortality was reduced from 5.9% to 4.5%, ($P < 0.001$). There was no difference in total major bleeding, 11.6% vs. 11.2% ($P = 0.434$), but higher occurrence of non-CABG related major bleeding 4.5% vs. 3.8% ($p = 0.026$). Episodes of dyspnoea were more common with ticagrelor, 14.2%, than clopidogrel, 9.2%, which led to discontinuation of treatment in respectively 1.0% and 0.3%. There was no difference in other important side effects. Treatment with ticagrelor instead of clopidogrel in a broad spectrum of patients with acute coronary syndrome provides a clinically important reduction in mortality and myocardial infarction without an increase in total major bleeding, but with a rise in non-procedure related bleeding.



Discussant see Presenter report
Steen Dalby Kristensen, FESC
(Denmark)

Report:

Ticagrelor compared with clopidogrel in patients with acute coronary syndromes – the PLATO trial presented by Lars Wallentin, ESC Congress Barcelona 2009. The new reversible oral P2Y12 receptor antagonist, ticagrelor, was compared to the ‘classic’ irreversible P2Y12 blocker clopidogrel in 18,264 patients with acute coronary syndromes (ACS) comprising a broad population with non-ST- or ST-elevation myocardial infarction (MI). Ticagrelor was superior to clopidogrel in terms of preventing the combination of cardiovascular death/ MI/stroke without causing a significant increase in major bleedings. Also, cardiovascular mortality, total mortality and the incidence of stent thrombosis were significantly reduced. There was an increased risk of non-procedure-related bleedings in the ticagrelor group. Ticagrelor has the potential to improve prognosis in patients with ACS.

Comments:

The investigators should be congratulated for this well-designed and nicely conducted landmark study. Overall, treating 54 patients for one year with ticagrelor instead of clopidogrel prevented one event of cardiovascular death, MI or stroke.

MI and Bleeding The authors used the new global MI definition and the trial design has been described previously (S James et al, Am Heart J 2009; 157: 599-605). A new definition of bleedings was used in PLATO. This definition seems appropriate and as good as the other 8-10 bleeding definitions that have been used in previous trials. There was no significant difference in PLATO or TIMI major bleedings between the two groups. However, there was an increased risk of non-CABG bleedings in the ticagrelor group, whereas the incidence of CABG-related bleedings did not differ. Patients with active bleeding, a bleeding history or severe anemia were excluded from the study, and therefore the bleeding profile of ticagrelor should also be tested in 'real' world ACS patients. One of the major advantages of a reversible inhibition of P2Y12 is indeed the possibility of reducing bleeding during surgery, and therefore it is not surprising that ticagrelor was not associated with an increased incidence of CABG related bleeds. Dosing and duration The dose of ticagrelor was chosen according to phase 2 trials (DISPERSE and DISPERSE-2) and clopidogrel was dosed according to guidelines. The inclusion of non-naïve clopidogrel patients in the study is appropriate as this is the real world, and because sub-analysis on these patients might provide useful information. Patients were included within the first 24 hours of ACS. In this phase, the risk of events is high, thus perhaps favouring the fast onset of strong platelet inhibition obtained with ticagrelor. The ESC Guidelines recommend dual anti-platelet therapy for 12 months in ACS. In PLATO, duration of treatment was 6 to 12 months. There was a significantly lower incidence of ischaemic events in the ticagrelor group both within the first 30 days and also in the period from 1 to 12 months. There is currently no evidence to recommend dual anti-platelet therapy beyond 12 month in ACS.

Side effects and compliance

The authors report an increase in the levels of uric acid, and also an increased frequency of dyspnoea and brady-arrhythmias in the ticagrelor group. Some of the side effect have been described in phase 2 studies with ticagrelor and were expected. No severe new side effects seemed to occur and only few patients had to stop ticagrelor due to side effects. The study drugs were discontinued prematurely in 23.4 and 21.5% of the patients in the ticagrelor and the clopidogrel groups, respectively. Ticagrelor does not require metabolic activation, causes stronger platelet inhibition and has a fast onset of action. However, the reversible receptor binding and a 12 h half-life necessitate twice-daily dosing, which might be a problem in patients, who are not fully compliant. The investigators reported that compliance was approximately 83% in each group. Implementation of ticagrelor might be troublesome in patients, who are unable to fully adhere to the prescribed drug therapy, because insufficient platelet inhibition increases the risk of stent thrombosis and other ischaemic events.

Effects of Valsartan on morbidity and mortality in uncontrolled hypertensive patients with high risk of cardiovascular events (KYOTO Heart Study)

Topics: Cardiovascular Disease Prevention - Risk Assessment and Management

Session number: 3582-3583

Session title: Effects of Valsartan on morbidity and mortality in uncontrolled hypertensive patients with high risk of cardiovascular events (KYOTO Heart Study)

Authors: Matsubara, Hiroaki - Ruschitzka Frank



Presenter | see Discussant report
Hiroaki Matsubara (Japan)

List of Authors:

H.Matsubara, T.Sawada, T.Takahashi, H.Yamada, B. Dahröf

Abstract: Aims

The objective was to assess the add-on effect of valsartan on top of the conventional treatment for high risk hypertension in terms of the morbidity and mortality.

Methods and results

The KYOTO HEART study was of a multicentre, Prospective Randomised Open Blinded Endpoint (PROBE) design, and the primary endpoint was a composite of fatal and non-fatal cardiovascular events (clinicaltrials.gov NCT00149227). 3031 Japanese patients (43% female, mean 66 years) with uncontrolled hypertension were randomized to either valsartan add-on or non-ARB treatment. Median follow-up period was 3.27 years. In both groups, blood pressure at baseline was 157/88 mmHg, and 133/76 mmHg at the end of study. Compared with non-ARB arm, valsartan add-on arm had fewer primary endpoints (83 vs 155; HR 0.55, 95% CI 0.42-0.72, p=0.00001).

Conclusion

Valsartan add-on treatment to improve blood pressure control prevented more cardiovascular events than conventional non-ARB treatment in high-risk hypertensive patients in Japan. These benefits cannot be entirely explained by a difference in blood pressure control.



Discussant see Presenter report
Frank Ruschitzka, FESC
(Switzerland)

A randomized trial of dabigatran, a oral direct thrombin inhibitor, compared to warfarin in 18,113 patients with atrial fibrillation at high risk of stroke

Topics: Atrial Fibrillation

Session number: 181-182

Session title: A randomized trial of dabigatran, a oral direct thrombin inhibitor, compared to warfarin in 18,113 patients with atrial fibrillation at high risk of stroke

Authors: Connolly, Stuart J - Camm, John

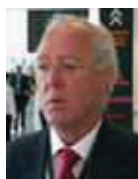


Presenter | see Discussant report
Stuart J Connolly, (Canada)

Abstract:

Background:

Warfarin reduces stroke in atrial fibrillation, but increases hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor. Methods: In a non-inferiority trial, 18,113 patients with atrial fibrillation at risk of stroke were randomized to blinded fixed doses of dabigatran 110 mg or 150 mg twice daily versus unblinded adjusted warfarin. Median follow-up was 2.0 years. The primary outcome was stroke or systemic embolism. Results: Rates of the primary outcome were 1.69% per year on warfarin versus 1.53% per year on dabigatran 110 mg (relative risk 0.91, 95% confidence interval 0.74 to 1.11; p [non-inferiority]<0.001) and 1.11% per year on dabigatran 150 mg (relative risk 0.66, 95% confidence interval 0.53 to 0.82; p [superiority]<0.001. Rates of major hemorrhage were 3.36% per year on warfarin versus 2.71% per year on dabigatran 110 mg (p=0.003) and 3.36% per year on dabigatran 150 mg (p=0.31). Rates of hemorrhagic stroke were 0.38% per year on warfarin versus 0.12% per year on dabigatran 110 mg (p<0.001) and 0.10% per year on dabigatran 150 mg (p<0.001). Mortality rates were 4.13% per year on warfarin versus 3.74% per year on dabigatran 110 mg (p=0.13) and 3.64% per year on dabigatran 150 mg (p=0.05). Conclusions: In patients with atrial fibrillation, dabigatran 110 mg was associated with similar rates of stroke and systemic embolism to warfarin, and lower rates of major hemorrhage. Dabigatran 150 mg was associated with lower rates of stroke and systemic embolism than warfarin, and similar rates of major hemorrhage.



Discussant see Presenter report
John Camm, FESC (United Kingdom)

Randomized trial of 3-limus agent-eluting stents with biodegradable or permanent polymer coating. ISAR-TEST-4 study

Topics: Acute Coronary Syndromes (ACS)

Session number: 1852-1853

Session title: Randomized trial of 3-limus agent-eluting stents with biodegradable or permanent polymer coating. ISAR-TEST-4 study

Authors: Mehilli, Julinda - Kugelmass, Aaron



Presenter | see Discussant report
Julinda Mehili (Germany)

List of Authors:

J. Mehilli, A. Kastrati, R.A. Byrne, S. Kufner, S. Massberg, K.A. Birkmeier, K-L. Laugwitz, S. Schulz, J. Pache, M. Fusaro, M. Seyfarth, A. Schömig



Discussant see Presenter report
Aaron Kugelmass
(United States of America)

Report:

Dr. Mehilli and colleagues are to be congratulated on the ISAR-TEST-4 trial. The study of over 2600 patients is the largest randomized trial of a biodegradable polymer based DES to date. The study population is comparatively “non-idealized”, and reflects real world practice with both stable angina and acute coronary syndrome patients. The population mirrors that of contemporary practice both clinically, (patients with diabetes, prior infarction and/or multivessel disease), and angiographically, (mean vessel size of 2.8 mm and greater than 70% B2 or C lesions). Current DES, which have durably reduced clinical and angiographic restenosis, utilize permanent polymers. It is thought that these polymers contribute to hypersensitivity reactions, ongoing inflammation, and thrombogenicity. Thus, current polymers likely contribute to delayed angiographic and clinical events such as late lumen creep, and delayed restenosis and stent thrombosis. Thus, the appeal of DES utilizing a biodegradable polymer. At both 30 days and twelve months, the biodegradable polymer stent was significantly non-inferior to available limus stents for both safety (cardiac death/MI) and clinical restenosis (TLR). Each of the contributing endpoints appeared similar. This is encouraging, but begets the question as to what is the appropriate clinical and angiographic surveillance period for biodegradable polymer stents. As is evident from DES, attempts to reduce vascular inflammation can result in temporal shifts in angiographic and clinical sequelae. Will the results of

biodegradable polymer stents prove as durable as current DES? Hopefully ISAR-TEST-4 includes longer term clinical and angiographic follow up. With additional follow up, this data can help drive this promising technology.

Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT- Study

Topics: Heart Failure (HF)

Session number: 3584-3585

Session title: Effects of Rolofylline in Patients with Acute Heart Failure Syndrome and Renal Impairment: Findings from the PROTECT- Study

Authors: Metra, Marco - Jessup, Mariell



Presenter | see Discussant report
Marco Metra, FESC (Italy)

List of Authors:

Metra M, O'Connor C, Massie B, Cotter G, Weatherley B, Dittrich H, Teerlink J, Bloomfield D, Ponikowski P. The PROTECT Executive Committee.

Abstract:

Background:

Patients hospitalized with acute decompensated heart failure (ADHF) often develop worsening renal function (WRF) and reduced diuretic response during their treatment. This clinical problem is associated with longer hospital stays and worse inpatient and post-discharge clinical outcomes. Recent studies have demonstrated that treatment with selective adenosine A1 antagonists (A1RA) can both enhance diuresis and prevent WRF. We hypothesized that early treatment with the A1RA, rolofylline, would facilitate early clinical improvement and reduce the risk of WRF and also reduce the rate of post-discharge death and readmissions for cardiovascular and renal causes. **Methods:** PROTECT was a multicenter, randomized (rolofylline vs placebo in a 2:1 ratio), double-blind, placebo-controlled trial in patients hospitalized for ADHF manifest by dyspnea at rest and signs of volume overload requiring iv loop diuretic therapy. Patients were anticipated to require ongoing IV furosemide 40 mg/day for at least 24 hours after enrollment and had to have impaired renal function (estimated creatinine clearance 20-80 mls/min). Additionally, patients were required to have a BNP level ≥ 500 pg/ml or NT-proBNP ≥ 2000 pg/ml. Key exclusions were ongoing or planned IV vasoactive therapy (except for nitrates), mechanical/circulatory support, ultrafiltration, dialysis, acute coronary syndromes within 2 weeks, severe

cardiac valve stenosis or high risk for seizures (a known adverse effect of A1RA). Randomization was to occur within 24 hours and rolofylline 30 mg/day IV or matching placebo was infused shortly thereafter for 4 hours/day for up to 3 days. The primary endpoint was a 3 category ordered outcome of treatment success, lack of change, or treatment failure, assessed through Day 7 or discharge. Treatment success was defined as moderate to marked improvement in dyspnea at both 24 and 48 hours after randomisation in the absence of treatment failure. Treatment failure included any of the following: death or readmission for HF through Day 7, worsening symptoms and/or signs of HF after Day 2 through 7 or discharge with the need for rescue therapy, persistent renal impairment (SCr increase ≥ 0.3 mg/dL through Day 7 confirmed at Day 14, or initiation of hemofiltration or dialysis through Day 7). Secondary endpoints included time to death or rehospitalization for cardiovascular or renal causes through Day 60 and the proportion of patients with persistent renal impairment (SCr increase ≥ 0.3 mg/dL from randomization to Day 7, confirmed at Day 14, initiation of hemofiltration or dialysis, or death up to day 7).

Results: Patients (n=2033) were randomized between May 2, 2007 and January 23, 2009 at 173 sites in North America, Argentina, Israel, Europe, and Russia to rolofylline (n=1356) and placebo (n=677). For the primary endpoint (Table 1), rolofylline was associated with more successes than placebo, but also more failure (odds ratio versus placebo 0.92, 95%CI 0.78, 1.09, p=0.348). The secondary composite endpoint of death or cardiovascular or renal hospitalization occurred in 30.7% of rolofylline patients (25.7% were hospitalized and 8.9% died) and 31.9% of placebo patients (25.6% were hospitalized and 9.5% died), yielding a time to first event hazard ratio of 0.98, 95% CI 0.83-1.17, p=0.86). Rolofylline did not reduce the incidence of renal impairment compared to placebo (15.0% vs 13.7%, respectively, odds ratio versus placebo 1.11, 95% CI 0.85, 1.46; p = 0.44. The number of patients experiencing one or more AE was similar between rolofylline (62.9%) and placebo (61.4%). However, more patients on rolofylline experienced nervous system disorders, with 11 patients (0.8%) experiencing seizure and 16 patients (1.2%) experiencing stroke on rolofylline, with no patients experiencing seizure and 3 patients (0.5%) experiencing stroke on placebo.

Table 1: Effects on Primary 3 Category Ordered Endpoint

	Rolofylline 30 mg N = 1356	Placebo N = 677
Success, 0% (n)	40.6 (551)	36.0 (244)
Unchanged, % (n)	37.5 (509)	44.2 (299)
Failure, % (n)	21.8 (296)	19.8 (134)

Conclusions: The primary efficacy endpoint of the study, that rolofylline 30 mg would provide a favorable shift in the distribution of the primary endpoint of success, unchanged, and failure compared to placebo was

not met. Nor were either of the two key secondary efficacy endpoints met. The overall safety profiles of the

Table 2: Dyspnea Improvement and Failure-Criteria

	Rolofylline 30 mg N = 1356	Placebo N = 677
Moderate or marked dyspnea improvement at both 24 and 48 hours % (n)	51.2 (694)	44.5 (301)
Components of treatment failure % (n)		
- Death / Day 7	1.7 (23)	2.1% (14)
- HF readmission / Day 7	0.4% (5)	0.6% (4)
- Workseing HF Day 7/discharge	9.1% (123)	9.7 (66)
- Persistent renal impairment	12.7% (172)	11.1 (75)
- SCr \geq 0.3 mg/dL (Day 7 and Day 14)	12.3% (167)	10.6% (72)
- Initiation of hemofiltration	0.4% (6)	0.9% (6)

placebo and rolofylline groups were similar. No increase in cardiac AEs were seen. However, treatment with rolofylline 30 mg was associated with a higher incidence of seizures and a trend towards more strokes.



Discussant see Presenter report
Mariell Jessup, FESC
(United States of America)

Clinical Efficacy and Safety of Otamixaban, an Intravenous, Selective Factor Xa Inhibitor for the Treatment of Non-ST-Elevation Acute Coronary Syndromes: Results of SEPIA-ACS1 TIMI 42

Topics: Acute Coronary Syndromes (ACS)

Session number: 183-184

Session title: Clinical Efficacy and Safety of Otamixaban, an Intravenous, Selective Factor Xa Inhibitor for the Treatment of Non-ST-Elevation Acute Coronary Syndromes: Results of SEPIA-ACS1 TIMI 42

Authors: Sabatine, Marc - White, Harvey



Presenter | see Discussant report
Marc Sabatine,
(United States of America)

List of Authors:

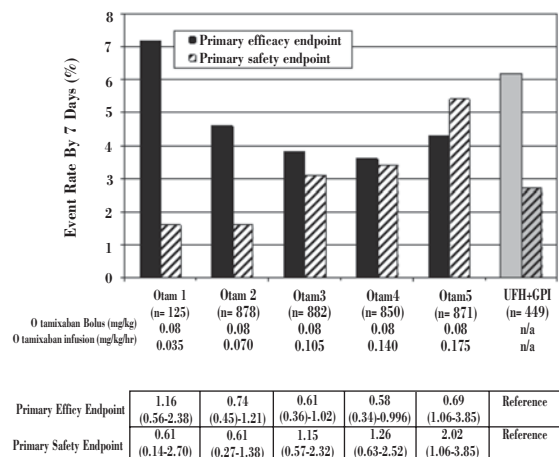
Marc S. Sabatine, MD, MPH on behalf of the SEPIA-ACS1 TIMI 42 Investigators

Abstract:

Background:

For many years, unfractionated heparin (UFH) has been the cornerstone of anticoagulant therapy for patients presenting with a non-ST-elevation acute coronary syndromes (NSTEMI ACS). However, UFH has numerous limitations, including being an indirect, non-selective

inhibitor of coagulation factors with unpredictable pharmacodynamic activity. In contrast, otamixaban is a novel, synthetic, intravenous, direct, selective inhibitor of Factor Xa with an initial half life of 30 minutes and predictable pharmacodynamic activity. **Methods:** We randomized 3241 patients within 24 hours of presentation of a NSTEMI ACS (with either an elevated biomarker of necrosis or ST segment deviation and in whom an invasive strategy was planned) to receive double-blinded treatment with one of 5 doses of otamixaban (0.08 mg/kg bolus followed by infusions ranging from 0.035 to 0.175 mg/kg/hr) or UFH + the glycoprotein IIb/IIIa inhibitor (GPI) eptifibatid (ClinicalTrials.gov unique identifier: NCT00317395). The primary efficacy endpoint was the composite of all-cause death, new myocardial infarction, severe recurrent ischemia requiring urgent revascularization, or bailout use of a GPI through day 7. The primary safety endpoint was TIMI major or minor bleeding unrelated to CABG. Dose arm 1 (lowest dose) was stopped early at the recommendation of the Data Safety Monitoring Committee due to inadequate anticoagulation; the remaining dose arms enrolled to scheduled completion. **Results:** The mean age of subjects was 61 years and 31% were female. A total of 99% underwent angiography, 63% underwent PCI, and 4% underwent CABG; 98% were treated with aspirin and 98% with clopidogrel. The rate of the primary efficacy and safety endpoints are shown in the Figure. There was no statistically significant difference in the rate of the primary efficacy endpoint across the otamixaban arms. However, in all of the otamixaban arms except dose arm 1, the point estimate for the primary efficacy endpoint favored otamixaban over UFH + GPI. Specifically, at intermediate doses (dose arm 3, 0.105 mg/kg/hr and dose arm 4, 0.140 mg/kg/hr) treatment with otamixaban resulted in approximately 40% reductions in the primary efficacy endpoint (RR 0.61, 95% CI 0.36-1.02 and RR 0.58, 95% CI 0.34-0.996, respectively) and approximately 45% reductions in death or MI (RR 0.52, 95% CI 0.28-0.98 and RR 0.56, 95% CI 0.30-1.03, respectively) as compared with UFH + GPI. There was a significant dose response in terms of the primary safety endpoint among the 5 otamixaban arms (P=0.0003), but the rate in otamixaban dose arms 3



& 4 (3.1-3.4%) were not significantly higher than the rate with UFH + GPI (2.7%). Conclusion: Otamixaban is a novel, synthetic, direct, selective inhibitor of Factor Xa that, at intermediate doses in patients presenting with NSTEMI ACS, may be associated with as much as a 40% lower risk of ischemic events and a comparable risk of bleeding compared with UFH + GPI. These data are encouraging for additional studies of otamixaban in patients with NSTEMI ACS.



Discussant see Presenter report
Harvey White, FESC (New Zealand)

Report:

The SEPIA-ACS1 TIMI 42 (Study to Evaluate the Pharmacodynamics, the Safety and Tolerability, and the Pharmacokinetics of Several Intravenous Regimens of the Factor Xa Inhibitor Otamixaban (XRP0673), in Comparison to Intravenous Unfractionated Heparin-Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction) trial is a well performed trial. It tested otamixaban which is a short acting intravenous direct factor Xa inhibitor with a half life of about 3 hours compared to unfractionated heparin (UFH) plus eptifibatide in patients with non-ST elevation acute coronary syndrome (NSTEMI ACS). The trial identified a signal for reduction in ischaemic events with otamixaban but also a signal associated with increased bleeding. This is an important study with a high rate of angiography (98%) and guideline recommended medications. The trial was a large dose ranging trial in 3241 patients with NSTEMI ACS following a dose ranging trial in 947 patients undergoing urgent PCI (SEPIA PCI trial). This is to be compared to a previous era when small numbers of patients were investigated in order to select a dose for a phase III trial e.g.: in GUSTO I <100 patients were tested with the streptokinase/TPA combination and in GUSTO IIa <50 patients were tested with the hirudin dose that was evaluated in GUSTO IIa. The patients enrolled in SEPIA-ACS1 were at high risk for ischaemia (ST deviation ≥ 0.1 mv in the UFH plus eptifibatide group 57%, elevated biomarker in the UFH plus eptifibatide group 79%) and underwent a planned early invasive strategy. The primary endpoint was a composite of death, MI, urgent revascularization and bailout IIb/IIIa antagonists for an ischaemic or thrombotic endpoint. Five doses of otamixaban were tested (0.08mg/kg bolus followed by infusions of 0.035, 0.070, 0.105, 0.140, or 0.175mg/kg/hr) or a control of UFH plus eptifibatide with a single bolus of eptifibatide rather than 2 boluses: 180ug/kg and infusion for 18-24 hours with renal adjustment. This is different to the double bolus 180ug/kg 10 minutes apart used in the ESPIRT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) and EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment

Elevation Acute Coronary Syndrome) trials and would not be expected to achieve blockade of greater than 90% of available glycoprotein IIb/IIIa receptors in more than 90% of patients. The primary safety endpoint was TIMI major or minor bleeding not related to CABG. This raises the question to what definition of bleeding should be used? There are many different definitions for bleeding. Also different bleeds have different meaning e.g.: intracranial haemorrhage has quite a different clinical meaning than a fall in haemoglobin. Over what time period should we capture the information about bleeding? Perhaps it should be 96 hours with PCI with a landmark analysis out to 30 days or 120 hours with medical treatment with a landmark analysis out to 30 days. Also is there an acceptable ceiling for major bleeding? In the EARLY ACS trial TIMI major bleeding with upstream eptifibatide was 2.6% at 120 hours vs 1.8% for patients who received eptifibatide in the catheterisation laboratory. Clearly we need a common template to be available so trials can be compared? There is also a need to have reversible agents so that once present bleeding can be stopped. Bleeding is associated with increased morbidity and mortality (OASIS 5) and it would seem reasonable to test a dose with decreased bleeding than control. Clearly there is much to be gained in capturing minor bleeding, but for selection of a drug dose to move into phase 3 trials, perhaps we should be more focused on what is a ceiling for unacceptable bleeding. This ceiling may be gleaned from major bleeding data and may be around the level of 2.6% with upstream eptifibatide as in EARLY ACS. The primary endpoint in SEPIA- ACS1 included adjudicated thrombotic and non-thrombotic procedural complications during the index PCI (including abrupt or threatened closure, new intracoronary thrombus, side branch closure, distal embolization, no-reflow, thrombus in catheter or adherent to guidewire, coronary dissection with decreased flow, difficulty in reaching or crossing lesion, unplanned stent use, suboptimal results, coronary perforation (tamponade). The 0.035mg/kg/hr dose was stopped because of clinical evidence of inadequate anticoagulation. The primary endpoint was reduced from 6.2% in the combined UFH plus eptifibatide arm 4.6%, 3.8%, 3.6% and 4.3% (P trend=0.34). For death and MI there was a similar approximately 57% reduction for the 4 doses of otamixaban (2.8%, 2.6%, 2.7%, 2.8%) compared with UFH plus eptifibatide. Rates of the primary safety endpoint of TIMI major and minor bleeding across the 5 otamixaban dose were 1.6%, 1.6%, 3.1%, 3.4% and 5.4% (P trend=0.0001); the rate in the control arm was 2.7%. Patients treated with 0.070mg/kg/hr tended to have higher rates of bailout glycoprotein IIb/IIIa inhibitor vs; 1.99, (95% CI 0.73-5.44). Whereas higher doses of otamixaban had similar use to that observed with UFH plus eptifibatide. In SEPIA-PCI there were 8 catheter thromboses. Perhaps supplemental UFH should be considered to prevent contact thrombosis with otamixaban as with the indirect factor X inhibitor fondaparinux (OASIS 5, OASIS 6). It would be interesting to know how many cases of new intracoronary, catheter or guidewire throm-

bus occurred in the current trial. In addition further information could be provided in respect of different loading doses of clopidogrel for both efficacy and bleeding and for the etiology of strokes; were some of these intracranial haemorrhages; 3 strokes occurred in the 0.105mg/kg/hr dose and 1 in the 0.07mg/kg/hr dose. Myocardial infarction was part of the composite endpoint and used the universal definition for MI and PCI but not for CABG where only 5x elevation of biomarkers or new Q waves was required and not both or evidence of new graft or native coronary artery occlusion. The universal redefinition of MI recommended that a universal definition template be available with different definitions and cutpoints for biomarkers and hopefully that will be available on line, so we can make comparisons with other trials. The investigators of the SEPIA-ACS1 trial suggested that "Otamixaban 0.105-0.140mg/kg/hr appears to be best range for further study as a replacement for UFH plus glycoprotein IIb/IIIa". However the lower dose of Otamixaban (0.07mg/kg/hr) had similar efficacy for the primary endpoint, and for death and MI. In addition it had the lowest bleeding compared with the next two doses (52%, 47% lower for major and minor bleeding) and 59% lower than control; 1.6% vs 2.7%. Importantly TIMI major bleeding was also similar in the 0.07mg/kg/hr group to control (1.8%) and 53%, 69% lower than the next two higher doses but there were increased thrombotic complications and 2.2% (1.1% control) use of IIb/IIIa antagonists compared with bivalirudin in the ACUTY trial where 7% of bailout IIb/IIIa antagonists were used. However this should be evaluated from the point of view as to whether hard clinical adverse events ensued. There continues to be an unmet need for patients with acute coronary syndromes for both ischaemia and the new paradigm for bleeding. SEPIA-ACS1 provides new information which will enable appropriate dose selection for a phase III trial.

Immediate angioplasty versus ischemia-guided management after thrombolysis for ST-segment elevation myocardial infarction in areas with very long transfers: The NORDISTEMI study

Topics: Acute Coronary Syndromes (ACS)

Session number: 1844-1845

Session title: Immediate angioplasty versus ischemia-guided management after thrombolysis for ST-segment elevation myocardial infarction in areas with very long transfers: The NORDISTEMI study

Authors: Halvorsen, Sigrun - Verheugt, Freek



Presenter | see Discussant report
Sigrun Halvorsen, FESC (Norway)

List of Authors:

Ellen Bøhmer, Pavel Hoffmann, Michael Abdelnoor, Harald Arnesen, Sigrun Halvorsen

Abstract:

Purpose:

Thrombolysis remains the treatment of choice in ST-segment elevation myocardial infarction (STEMI) when primary PCI cannot be performed within 90-120 min. The efficacy and safety of early PCI after thrombolysis is still unclear. The aim of this study was to compare a strategy of immediate transfer for PCI after thrombolysis to an ischemia-guided approach, in patients with very long transfer distances. **Methods:** 266 patients with acute STEMI of < 6 h duration, living in rural areas in Norway with 100 - 400 km transfer distances to PCI were treated with full-dose tenecteplase, aspirin, enoxaparin and clopidogrel. Patients were randomized to immediate transfer for PCI, or to conservative management in the community hospitals with urgent transfer only if rescue indication or clinical deterioration. The primary outcome was a composite of death, reinfarction, stroke or new ischemia within 12 months, and analysis was by intention to treat. **Results:** The primary endpoint at 12 months was reached in 28 patients (21 %) in the early invasive group compared with 36 (27 %) in the conservative group (hazard ratio 0.72, 95% CI 0.44-1.18, p=0.19). The composite of death, reinfarction or stroke at 12 months was significantly reduced in the early invasive compared to the conservative group (6.0% versus 16%, hazard ratio 0.36, 95% CI 0.16-0.81, p=0.01). No significant differences in bleeding or infarct size were observed, and transport complications were few. **Conclusions:** Immediate transfer for PCI after thrombolysis did not improve the primary outcome significantly, but reduced the rate of death, reinfarction or stroke within 12 months compared to conservative treatment.



Discussant see Presenter report
Freek Verheugt, FESC (Netherlands)

Unprotected left main revascularization in patients with acute coronary syndromes. GRACE left main study

Topics: Acute Coronary Syndromes (ACS)

Session number: 1846-1847

Session title: Unprotected left main revascularization in patients with acute coronary syndromes. GRACE left main study

Authors: Montalescot, Gilles - Hamm, Christian



Presenter | see Discussant report
 Gilles Montalescot (France)



Discussant see Presenter report
 Christian Hamm, FESC (Germany)

Report:

In patients with acute coronary syndromes undergoing coronary angiography main stem lesions are found in approximately 5% of the cases. The treatment decision in this high risk subset is regularly difficult, because surgery in developing myocardial infarction is problematic and angioplasty technically demanding. Evidence for treatment decisions in such scenarios cannot be derived from randomised trials, but must come from carefully conducted registries. In this context, the GRACE data provide valuable information for the management of these patients. It is self explaining that the mortality is high and the confounding factors are too complex to make conclusions with respect to the best treatment modality. The decision making has to be very individual and depends also on the local expertise and circumstances. There is a strong trend over the observation period of 7 years to acutely perform more angioplasties and to delay surgery to following days. Therefore, these data reassure of what is currently done across the world and support the use of revascularisation techniques whatever and whenever feasible.

Primary angioplasty versus fibrinolysis in the very elderly. The TRIANA Study

Topics: Acute Coronary Syndromes (ACS)

Session number: 1848-1849

Session title: Primary angioplasty versus fibrinolysis in the very elderly. The TRIANA Study

Authors: Bueno, Hector - Dudek, Dariusz



Presenter | see Discussant report
 Hector Bueno, FESC (Spain)

List of Authors:

Héctor Bueno, Joaquín J. Alonso, Amadeo Betriu, Angel Cequier, Eulogio J. Garcia, Magda Heras, Jose L.

Lopez-Sendon, Carlos Macaya, Rosana Hernandez-Antolin, on behalf of the TRIANA investigators, Spanish Society of Cardiology, Madrid, Spain

Abstract:

Background:

Primary angioplasty (PCI) is currently considered the preferred reperfusion therapy for STEMI. However, data on clinical outcomes comparing primary PCI vs. fibrinolysis in very old patients are scarce.

Methods:

The TRIANA study (clinicaltrials.gov# NCT00257309) is a Spanish multicenter randomized trial comparing primary PCI versus a conservative strategy consisting in fibrinolysis (weight-adjusted TNK+UFH) and rescue PCI. Included patients were 75 years of age or older presenting within 6 hours after STEMI. Patients with accepted contraindications for fibrinolysis and those with any previous cerebrovascular event, cardiogenic shock or blood pressure >180/110 mmHg at any time during the event were excluded. The primary endpoint was the composite of all-cause death, recurrent myocardial infarction, or disabling stroke at 30 days. Secondary endpoints were recurrent ischemia leading to revascularization, and major bleeding. Events were adjudicated by an "ad hoc" committee blinded to the study treatments.

Results:

The trial was prematurely stopped due to slow recruitment, after enrolling 266 out of the 560 planned patients. Mean age was 81 years and 56% men. The two treatment groups were well balanced with regard to demographic characteristics and risk factors. Outcomes at 30 days were as follows. After one-year follow-up, results tended to equate.

	Primary PCI (n=132)	Fibrinolysis (n=134)	Odds Ratio (95% CI)	P Value
Primary Endpoint	25 (18.9%)	34 (25.4%)	1.46 (0.81-2.61)	0.21
Death	18 (13.6%)	23 (17.2%)	1.31 (0.67-2.56)	0.43
Reinfarction	7 (5.3%)	11 (8.2%)	1.60 (0.6-4.25)	0.35
Disabling stroke	1 (0.8%)	4 (3.0%)	4.3 (0.44-36.5)	0.18
Recurrent ischemia	1 (0.8)	13 (9.7%)	14.1 (1.8-109)	<0.001
Major bleed	5 (3.8%)	5 (3.7%)	0.98 (0.28-3.48)	0.98

Conclusions:

In spite of the sample size limitation, this trial shows a trend towards a lower mortality, reinfarction and disabling stroke in elderly patients undergoing primary PCI compared with fibrinolysis. In addition, recurrent ischemia is dramatically reduced by primary PCI. Therefore, this approach might also be recommended for the oldest patients presenting with STEMI.

Discussant see Presenter report
 Dariusz Dudek, FESC (Poland)

Routine upfront abciximab versus standard peri-procedural therapy in patients undergoing primary percutaneous coronary intervention for cardiogenic shock. The PRAGUE-7 Study

Topics: Acute Coronary Syndromes (ACS)

Session number: 1850-1851

Session title: Routine upfront abciximab versus standard peri-procedural therapy in patients undergoing primary percutaneous coronary intervention for cardiogenic shock. The PRAGUE-7 Study

Authors: Widimsky, Petr - Lafont, Antoine



Presenter | see Discussant report
Petr Widimsky, FESC
(Czech Republic)

List of Authors:

Petr Tousek, Richard Rokyta, Jitka Tesarova, Radek Pudil, Jan Belohlavek, Josef Stasek, Filip Rohac and Petr Widimsky

Abstract:

Background:

The outcome of acute myocardial infarction (AMI) complicated with cardiogenic shock is poor. Early mechanical revascularization is superior to medical treatment, but the mortality remains high. Registries have shown benefit from administration of GPIIb/IIIa inhibitors during primary percutaneous coronary intervention (PCI) in patients with cardiogenic shock. The aim of this study was to analyse, whether upfront abciximab administration (when compared with standard therapy) improves the outcomes of cardiogenic shock. **Methods:** This multicentre open trial randomized 80 patients (mean age 66 years) with AMI complicated by cardiogenic shock (25% after cardiopulmonary resuscitation, 46% on mechanical ventilation) expected to undergo primary PCI into group A (routine upfront – pre-procedural - abciximab bolus followed by 12-hours abciximab infusion) and group B (standard therapy with optional abciximab administration according to the interventional cardiologist). The study primary objective was 30-day combined outcome (death / reinfarction / stroke / new renal failure). Secondary objectives were: left ventricular ejection fraction assessed by echocardiography on day 30, major bleeding complications, myocardial blush grade (MBG) after PCI, TIMI-flow after PCI.

Results:

PCI was technically successful in 90% (A) vs. 87.5% (B) patients. Abciximab was used in 100% (A) vs. 35% (B). The primary endpoint occurred in 17 group A patients (42.5%) and 11 group B patients (27.5%, $p = 0.24$). Fifteen patients (37.5%) died during hospitaliza-

tion in group A vs. 13 patients (32.5%) in B ($p = 0.82$). Ejection fraction among survivors after 30 days was $44 \pm 11\%$ (A) vs. $41 \pm 12\%$ (B, $p = 0.205$). Major bleeding occurred in 17.5% (A) vs. 7.5% (B, $p = 0.310$) and stroke in 2.5% (A) vs. 5% (B). No differences (A vs. B) were found in TIMI-flow and MBG after PCI.

Conclusions:

This study did not show any benefit from routine pre-procedural abciximab when compared with a selective abciximab use during the PCI procedure.



Discussant see Presenter report
Antoine Lafont, FESC (France)

Report:

The Prague 7 trial is a multicenter, open, randomized study evaluating the use of Abciximab as upfront strategy with primary angioplasty in patients with acute myocardial infarction (AMI) with cardiogenic shock (CS). The primary endpoint was a 30-day combined criterion (death / reinfarction / stroke / new renal failure). The secondary endpoints were left ventricular ejection fraction assessed by echocardiography on day 30, major bleeding complications, myocardial blush grade after PCI, and TIMI-flow after PCI. The strategy facilitating primary percutaneous coronary intervention (PCI) with Abciximab in the Prague 7 study is logical since the TIMI flow appears as a major prognostic factor, influencing dramatically the mortality rate, and is greatly improved by Abciximab in several non randomized studies with CS, and randomized studies excluding CS. However, the Prague 7 trial failed to show benefit from routine pre-procedural Abciximab when compared to a selective Abciximab use during the PCI procedure. What are the reasons to explain the failure of PRAGUE 7 ? At first, authors must be acknowledged to perform a new trial in the setting of AMI with CS: indeed, inclusion of this population is a major challenge, and they were able to fulfill their goal with only 4 centers while ten years earlier, the randomized SMASH trial was stopped because of lack of recruitment of more than 55 patients involving 9 centers. The editorial entitled “Randomized trials in cardiogenic shock, what’s the problem?” in 1999, underlined the difficulties to perform randomized studies in AMI with CS. Prague 7 suffered from lack of statistical power, and the particular difficulty of recruiting this very special population. In that matter, the study population recruited was too heterogeneous, not reflecting the standard CS population described in the registries, namely an ejection fraction of 44 vs 41% one month after revascularization which is higher than expected in this special population. The criteria of inclusion were too large. Of note, the high percentage of resuscitated patients (which were excluded

in the SMASH study) represents a particular population, distinct from that of patients with CS complicating AMI. The definition of AMI was not restricted to ST+, rendering more heterogeneous the studied population: namely, the extent of ST- AMI was 20% vs 5% between the control and the study group, i.e., 80% vs 70% ST+ patients, respectively. The randomization process (using alternate days and not a series of random numbers) does not guarantee the masking of randomization to clinician and results in imbalance between the 2 groups on some important prognostic factors: the door to balloon time, a key parameter for comparing the 2 groups, was significantly increased in the control group (60 vs 35 min, $p=0.017$) reflecting a bias attributable to a failure of randomization, and impairing the interpretation. The lack of power calculation, led to both an arbitrary number of patients and probably a lack of statistical power. As the authors clearly recognized, the lack of results may be incriminated to the small size of the population. The 35% crossover might also have participated to the lack of power of the trial. These limitations should be taken into account when analyzing the main result: no angiographic benefit attributable to Abciximab, a finding in opposition to the previous results from non randomized studies in CS that showed high procedural success rate. Not only there was no improvement of the TIMI flow before PCI, but also after PCI in the study group. ; in ADMIRAL, CS patients with Abciximab ($n=11$) presented with a TIMI 3 flow in 100% vs 83.3% in the control group ($n=14$) 24 hours after the procedure. Even if it was not significant, this translated in a 6-month mortality rate of 9.1 vs 21.4%, and could represent a basis for power calculation. For both questionable internal validity and lack of power, these results cannot be conclusive with regards to the hypothesis. Ten years after SMASH, they remind us that evaluating therapeutic strategies in patients with CS complicating AMI is still a huge challenge for trialists.

A randomized evaluation of irbesartan versus placebo in patients with Atrial Fibrillation (factorial design of ACTIVE Program)

Topics: Atrial Fibrillation

Session number: 3586-3587

Session title: A randomized evaluation of irbesartan versus placebo in patients with Atrial Fibrillation (factorial design of ACTIVE Program)

Authors: Yusuf, Salim - Brugada Terradellas, Josep



Presenter | see Discussant report
Salim Yusuf, FESC (Canada)

List of Authors:

S. Yusuf and S. Connolly on behalf of the ACTIVE Investigators. Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

Abstract:

One of the strongest risk factors for the development of atrial fibrillation (AF) is elevated blood pressure (BP). Stroke and heart failure which are common complications of AF are also related to elevated BP. Small trials have suggested that blockade of RAAS may be beneficial in AF. However, BP lowering or blockade of RAAS, has not been studied in large trials of patients with AF. We evaluated the comparative effects of irbesartan, an angiotension receptor blocker, (target dose 300mg/day) or placebo given for a mean of 4.1 years, in reducing major vascular events (CV death, MI or stroke: first co-primary) and heart failure (CV death, MI stroke: second co-primary) in 9016 patients with AF receiving usual care. These patients were drawn from two parallel trials (ACTIVE-A and ACTIVE-W) involving over 14,000 patients utilizing a partial factorial design. BP at entry was 138/75 mm Hg; mean age was 69.5 years. The reduction in BP was modest (-2.6/-1.9 mm Hg) with irbesartan compared to placebo. Irbesartan did not reduce the risk of the first co-primary outcome of CV death, myocardial infarction or stroke (5.4% per year in each group), but there was a lower rate of the second co-primary CV death, MI, stroke and heart failure hospitalizations (7.3% vs 7.7% $p=0.12$) with irbesartan, which was chiefly due to a significant reduction in the risk of heart failure hospitalization (3.2% per year in the placebo group versus 2.7% with irbesartan by 14%, $p=0.018$). Recurrent event analysis of the second co-primary (39.6% with irbesartan vs. 44.3% with placebo) indicated clearer differences (RR = 0.89, CI = 0.82 to 0.98 ; $p=0.06$). Post hoc analysis indicated a significant reduction in the risk of the composite of stroke, non-central nervous system embolism and transient ischemic attacks (3.4% per year in the placebo group versus 2.9% with irbesartan) by 13% ($p=0.02$), with consistently lower rates of each component of the composite. The number of admissions in hospital (4055 placebo vs. 3816 irbesartan; $p=0.004$) and days hospitalized for cardiovascular reasons were significantly reduced (39,941 placebo vs. 36,480 irbesartan; $p=0.0001$). Irbesartan was well tolerated with similar rates of drug discontinuation compared to placebo.

Conclusions:

The modest BP lowering achieved with irbesartan in this “normotensive” population with AF was associated with reductions in heart failure hospitalizations and thromboembolic events, but not in death or myocardial infarction. These findings suggest that the impact of larger degrees of BP lowering are worth exploring and may potentially lead to larger reductions in thromboembolic events and heart failure.



Discussant see Presenter report
Josep Brugada Terradellas, FESC
(Spain)

European CRT Survey

Topics: Heart Failure (HF)

Session number: 3588-3589

Session title: European CRT Survey

Authors: Bogale, Nigussie - Daubert, Jean-Claude



Presenter | see Discussant report
Nigussie Bogale, (Norway)

List of Authors:

Kenneth Dickstein, Nigussie Bogale, Silvia Priori, Angelo Auricchio, John G. Cleland, Anselm Gitt, Tobias Limbourg, Cecilia Linde, Dirk J van Veldhuisen, Josep Brugada

Abstract:

European Cardiac Resynchronization Therapy Survey.

Aims:

The European CRT Survey is a joint initiative taken by the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the European Society of Cardiology. The primary aim of this Survey is to describe current European practice associated with CRT implantations.

Methods and results:

141 centres from 13 European countries contributed data from consecutive patients successfully implanted with a CRT device with or without an ICD between November 2008 and June 2009.

2438 patients were enrolled. The median age of patients was 70 years (IQR 62-76) and 31 % were \geq 75 years. 78 % were in NYHA functional class III or IV and 22 % in I or II. The mean ejection fraction was 27 ± 8 and the mean QRS duration $157 \text{ ms} \pm 32$. QRS duration was $< 120 \text{ ms}$ in 9 %. Atrial fibrillation was reported in 23 %.

26 % of patients had a previously implanted permanent pacemaker or ICD. 76 % of procedures were performed by an electrophysiologist. 82 % had an elective admission for implantation and the median duration of hospitalisation was 3 days (IQR 2-7). 73 % received a CRT-D device which was more often implanted in men, younger patients and with ischaemic aetiology. The mean QRS duration was

reduced to $133 \text{ ms} \pm 27$ ($p < 0.0001$) at discharge. Peri-procedural complication rates were comparable to the rates reported in randomized trials.

Conclusion:

This CRT Survey provides important information describing current European practice with regard to patient demographics, selection criteria, procedural routines and status at discharge. These data should be useful for benchmarking individual patient management and national practice against wider experience.



Discussant see Presenter report
Jean-Claude Daubert, FESC (France)

Prevention of Sudden Cardiac Death in Post Myocardial Infarction Patients: Risk Stratification, ICD Therapy Penetration and Related Longterm Outcome: Final Results of the German PreSCD II Registry

Topics: Sudden Cardiac Death and Resuscitation

Session number: 3590-3591

Session title: Prevention of Sudden Cardiac Death in Post Myocardial Infarction Patients: Risk Stratification, ICD Therapy Penetration and Related Longterm Outcome: Final Results of the German PreSCD II Registry

Authors: Voeller, Heinz - Vardas, Panagiotis



Presenter | see Discussant report
Voeller, Heinz, FESC (Germany)

List of Authors:

H. Völler, W. Kamke, H. U. Klein, M. Block, R. Reibis, S. Treusch, K. Contzen, K. Wegscheider

Abstract:

Current guidelines recommend implantable cardioverter-defibrillator (ICD) therapy for primary prevention of sudden cardiac death (SCD) in patients with reduced left ventricular function (LVEF = 30-35%) more than 40 days after myocardial infarction (MI). The aim of the prospective Prevention of Sudden Cardiac Death II (PreSCD II) registry was to investigate daily practice of ICD therapy in post-MI patients and to evaluate their long-term survival. Methods: 10,612 consecutive post MI patients (61 ± 12 years, 76% male) were enrolled in 19 cardiac rehabilitation (CR) centers in Germany from December 2002 to May 2005. All patients with LVEF = 40% together with a

random subsample with preserved left ventricular function (LVEF > 40%) were followed for 36 months. Logistic regression modeling was applied to characterize patients with ICD therapy. Cox proportional hazard models with ICD therapy as time-dependent covariate were used to study overall survival. Results: 77.4% of all patients were enrolled within 60 days, 10.7% more than one year after MI. 269 patients (2.5%, Group 1) had LVEF = 30% and 727 patients (6.9%, Group 2) had LVEF 31-40%. Follow-up was performed in a total of 2,058 patients, 259 in Group 1, 693 in Group 2 and 1,106 in Group 3 (LVEF > 40%). Seventy-five patients received an ICD within four months after risk stratification, 57 (22%) in Group 1 and 15 (2.2%) in Group 2. After 36 months 142 (6.9%) patients had received an ICD, 47% of them within one year after their index MI. ICD implantation was mainly driven by LVEF = 30% and to a lesser extent by non-sustained ventricular tachycardia, prior syncope, NYHA II-IV, prolonged QRS, renal insufficiency, and more remote index MI. ICD patients had an adjusted 44% lower mortality (HR 0.56, 95% CI 0.32-1.01; p=0.053) than comparable patients without ICD therapy. There was a significant trend towards lower mortality of ICD recipients if the device was implanted in the remote phase of MI (p<0.001). Conclusions: The PreSCD II registry showed a low prevalence of patients with reduced left ventricular function after MI. Few patients with guideline-based ICD indication received ICD therapy. Mortality was reduced if an ICD was implanted late after MI.



Discussant see Presenter report Vardas, Panagiotis FESC (Greece)

Report:

Access the slides from the discussant

Reduction in the risk of heart failure with preventive cardiac resynchronization therapy: MADIT-CRT Trial

Topics: Heart Failure (HF)

Session number: 3592-3593

Session title: Reduction in the risk of heart failure with preventive cardiac resynchronization therapy: MADIT-CRT Trial

Authors: Moss, Arthur J - Breithardt, Guenter



Presenter | see Discussant report Arthur J Moss, (United States of America)

List of Authors:

Arthur J. Moss; W. Jackson Hall; David S. Cannom; Helmut Klein; Mary W. Brown; James P. Daubert; N.A. Mark Estes III; Elyse Foster; Henry Greenberg; Steven L. Higgins; Marc A. Pfeffer, David Wilber; Wojciech Zareba

Abstract:

This trial was designed to determine if cardiac resynchronization therapy would reduce mortality and heart failure events in patients with mild cardiac symptoms, reduced ejection fraction, and wide QRS complex

Methods:

Over the course of 4.5 years, we enrolled and followed 1820 patients with ischemic or nonischemic cardiomyopathy, ejection fraction 0.30 or less, QRS 130 ms or more, and New York Heart class I or II symptoms. Patients were randomly assigned in a 3:2 ratio to receive cardiac resynchronization therapy with defibrillator (1089 patients) or an implanted defibrillator (731 patients). The primary end point was all cause mortality or heart failure event, whichever occurred first.

Results:

During an average follow-up of 2.4 years, 17.2 percent of patients in the resynchronization group and 25.3 percent in the defibrillator group experienced a primary end point. The hazard ratio in favor of resynchronization therapy was 0.66 (95 percent confidence interval, 0.52 to 0.84; P=0.001), with similar benefit in patients with ischemic and nonischemic cardiomyopathy. Superiority of cardiac resynchronization therapy was driven by 41 percent reduction in the risk of a first heart failure event, a finding that was evident primarily in patients with QRS of 150 ms or more. Resynchronization therapy was associated with significant reduction in left ventricular volumes and improvement in ejection fraction. Serious adverse events were infrequent.

Conclusion:

Cardiac resynchronization therapy decreases the risk of heart failure events in relatively asymptomatic patients with low ejection fraction and wide QRS complex. This therapy provides effective prevention for heart failure in these at-risk cardiac patients.



Discussant see Presenter report Breithardt, Guenter (Germany)

Report:

Cardiac resynchronisation therapy (CRT) induces

progressive reverse LV remodeling and slows disease progression in patients with NYHA class III or IV heart failure. Whether it may also be beneficial in patients with less severe heart failure, was tested in the the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy) presented by A. Moss during the Hot Line Session. The trial randomised 1820 NYHA class I or II patients to CRT or no CRT. All patients were candidates for an ICD, had to have a QRS width of 0.13s or greater and a left ventricular ejection fraction of 0.30 or less. During follow-up, 17.2% of patients in the resynchronization group and 25.3 % in the ICD group experienced the primary end point of all cause mortality or a heart failure event whichever occurred first (Hazard Ratio 0.66, 95% confidence interval 0.52 to 0.84; P=0.001), with similar benefit in patients with ischemic and non-ischemic cardiomyopathy (10). Superiority of resynchronization therapy was driven by a 41% reduction in the risk of a first heart failure event without an effect on the 3% annual mortality in each treatment group. Resynchronization therapy was associated with significant reduction in left ventricular volumes and improvement in ejection fraction. Conclusions MADIT-CRT has shown that CRT may delay disease progression in heart failure class I or II patients through left ventricular remodeling. This is consistent with a prior smaller trial (REVERSE, 610 patients) that did, however, not reach statistical significance of a heart failure clinical composite response which compared only the percentage of patients worsened (primary end point). However, secondary endpoints were in line with the much larger MADIT-CRT trial results concerning left ventricular remodelling and reduction in the need for heart failure hospitalisations. CRT is an effective therapy in improving heart failure related manifestations in patients with poor left ventricular function (EF <0.30 like in MADIT-CRT or <0.40 like in REVERSE) who frequently are eligible for primary prevention ICD implantation with an ischemic or non-ischemic aetiology and broad QRS complexes of >0.12 s (REVERSE) or >0.13 s (MADIT-CRT) but with no or only minimal symptoms. Open Issues Is the evidence similarly strong for class I and II patients? This and other questions might be answered by merging the original data from both trials into a meta-analysis. Patient characteristics were not much different from previous ICD trials, especially with regard to ejection fraction. Should we re-define the present guidelines for primary ICD implantation to include CRT and, if so, to all patients with a QRS duration of >0.13s (or >0.12s like in REVERSE)? Or should there be a cut-off of about 0.15s as suggested by the subgroup analyses in both trials? Should parameters of dyssynchrony be added? Mortality in class I and II heart failure patients is low. However, if progression of the disease on the long-term is retarded by CRT, does this translate into a lower mortality as the disease would normally progress and as long as no competing risks occur? It may be difficult to find an answer to this issue since the present

data by MADIT-CRT but also REVERSE may make it at least difficult if not impossible to do another randomised trial with and without CRT which, as a mortality trial, would require a very large population.

**B-CONVINCED. Beta-blocker
CONTinuation Versus INTerruption in
patients with Congestive heart failure
hospitalized for a decompensation episode**

Topics: Heart Failure (HF)

Session number: 1025-1026

Session title: B-CONVINCED. Beta-blocker CONTinuation Versus INTerruption in patients with Congestive heart failure hospitalized for a decompensation episode

Authors: Jondeau, Guillaume - Swedberg, Karl



Presenter | see Discussant report
Guillaume Jondeau, FESC (France)

List of Authors:

Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, Jegou A, Bauer F, Trochu JN, Bouzamondo A, Tanguy ML, Lechat P, for the B-CONVINCED investigators

Abstract:

Whether or not beta-blocker therapy should be stopped during acutely decompensated heart failure (ADHF) is unsure. In a randomised, controlled, open labelled, non inferiority trial, we compared beta-blockade continuation versus discontinuation during ADHF in patients with LVEF below 40% previously receiving stable beta-blocker therapy. 169 patients were included, among which 147 were evaluable. Mean age was 72±12 years, 65% were males. After 3 days, 92.8% of patients pursuing beta-blockade improved for both dyspnea and general well being according to a physician blinded for therapy vs. 92.3% of patients stopping beta-blocker. This was the main end point and the upper limit for unilateral 95% CI for the difference (6.6%) is lower than the predefined upper limit (12.5%), indicating non-inferiority. Similar findings were obtained at 8 days and when evaluation was made by the patient. Plasma BNP at day 3, length of hospital stay, re-hospitalisation rate and death rate after 3 months were also similar. Beta-blocker therapy at 3 months was given to 90% of patients vs. 76% (p<0.05). During ADHF, continuation of beta-blocker therapy is not associated with delayed or lesser improvement, but with a higher rate of chronic prescription of beta-blocker therapy after 3 months, the benefit of which is well established.



Discussant see Presenter report
Karl Swedberg, FESC (Sweden)

The impact of achieved heart rate and reduction in heart rate on cardiovascular outcomes: an analysis of the Ivabradine arm of the BEAUTIFUL trial

Topics: Chronic Ischaemic Heart Disease (IHD)

Session number: 1027-1028

Session title: The impact of achieved heart rate and reduction in heart rate on cardiovascular outcomes: an analysis of the Ivabradine arm of the BEAUTIFUL trial

Authors: Fox, Kim - Boehm, Michael



Presenter | see Discussant report
Kim Fox, FESC (United Kingdom)



Discussant see Presenter report
Michael Boehm, FESC (Germany)

Report:

The BEAUTIFUL trial was a double-blind, placebo-controlled randomized trial on 10917 patients with documented coronary artery disease and left ventricular dysfunction (EF < 40%). Patients were randomized to ivabradine or placebo on top of evidence based treatments. In the overall population of BEAUTIFUL, heart rate reduction by ivabradine did not reduce the primary composite endpoint of cardiovascular death, admission to hospital for acute myocardial infarction or admission to hospital for new onset or worsening of heart failure. Interestingly, 28% of patients on ivabradine discontinued drug treatment mainly due to bradycardia and there was only a 5,6 bpm difference in heart rate between placebo and ivabradine at the end of the study in the total population. Therefore, the present subanalysis of the BEAUTIFUL data aimed at investigating whether heart rate response evaluated by heart rate change from baseline to one month and heart rate achieved at one month was predictive to evaluate outcomes in this patient population. Heart rate difference and heart rate achieved were evaluated as quartiles in those patients at a baseline heart rate above 70 bpm and on treatment

with ivabradine. The major strength of the analysis and the BEAUTIFUL programme in general is the clear physiological rationale of heart rate reduction. Heart rate is associated with cardiovascular outcomes in patients with vascular disease and chronic heart failure. Furthermore, the BEAUTIFUL population offers opportunity to observe high rates of vascular reevents as well as a progression of impaired left ventricular function to overt heart failure. The subanalysis of BEAUTIFUL asked a clear question, because the high rate of discontinuations (28%) and a small difference between placebo and ivabradine (5,6 bpm) in the total population of BEAUTIFUL might have represented one cause of missing the primary composite. Thus, there was need to further analyze the effects of certain degrees of heart rate lowering in this population. The subgroup was taken, in which a clear association of outcomes to a heart rate above 70 bpm was shown in BEAUTIFUL. This way of analysis could have been hampered by selection bias. It has to be pointed out that a subgroup of the whole BEAUTIFUL population (> 70 bpm) was further divided into a subgroup of ivabradine treatment and finally further divided of four subgroups of quartiles of different heart rates achieved and in quartiles of different heart rate changes. Therefore, the study stepwise formed subgroups which might introduce a selection bias. Heart rate responses at one month was related to cardiovascular outcomes over the whole study period. The open question remains here what is the risk in patients with long lasting heart rate reduction or fading heart rate reduction later. Interestingly, there was a clear association of achieved heart rates and heart rate responses at one month to vascular endpoints like hospitalization for acute myocardial infarction as well as to the progression to heart failure as evidenced by admission to hospital for new onset or worsening of heart failure. This contrasts to the total BEAUTIFUL population in which the heart failure related endpoints were not significantly associated with heart rate. However, this rigorous and more detailed analysis has raised the hypothesis that heart rate reduction in patients with higher heart rates might be beneficial also in the heart failure population, which is currently investigated in the SHIFT trial. However, it remains open whether outcome is better in those patients who are able to respond to heart rate lowering with ivabradine or whether the reduced event rate is due indeed to pharmacological effect of heart rate lowering by ivabradine itself. Therefore, the subanalysis of the BEAUTIFUL data is a very strong and clear hypothesis generating analysis. It has to be verified prospectively in trials on patients with heart failure and coronary artery disease taking into account the achieved heart rates and the amount of heart rate reduction.

Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial

Topics: Atrial Fibrillation

Session number: 1029-1030

Session title: Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial

Authors: Maggioni, Aldo Pietro - Crijns Harry



Presenter | see Discussant report
Aldo Pietro Maggioni, FESC (Italy)

List of Authors:

Aldo P. Maggioni, Gianna Fabbri, Donata Lucci, Roberto Marchioli, Maria Grazia Franzosi, Roberto Latini, Gian Luigi Nicolosi, Maurizio Porcu, Franco Cosmi, Severo Stefanelli, Gianni Tognoni, Luigi Tavazzi on behalf of the GISSI-HF Investigators

Abstract:

Aims: This ancillary analysis of the GISSI-HF database aims at assessing the effect of rosuvastatin on the occurrence of atrial fibrillation (AF) in patients with chronic heart failure (HF) who were not in AF at study entry.

Methods and Results:

GISSI-HF was a double-blind, placebo-controlled trial testing n-3 PUFA and rosuvastatin versus corresponding placebos in patients with chronic HF. AF occurrence was defined as presence of AF in the electrocardiogram performed at each visit during the trial or AF as a cause of worsening HF or hospital admission or as an event during hospitalization. Among the 3690 patients (80.7%) without AF on their baseline electrocardiogram, 15.0% developed AF during a median follow-up period of 3.7 years, 258 randomized to rosuvastatin (13.9%) versus 294 allocated to placebo (16.0%). While the difference was not significant at unadjusted ($p=0.097$) and multivariable analysis adjusting for clinical variables ($p=0.067$), it became significant after adjustment for clinical variables and laboratory examinations ($p=0.039$), clinical variables, laboratory examinations and background therapies ($p=0.038$).

Conclusion:

This study shows that there is some evidence of a beneficial effect of rosuvastatin in terms of reduction of AF occurrence in patients with HF. Larger populations are needed to provide a definite answer to the question.



Discussant see Presenter report
Harry Crijns, FESC (Netherlands)

Report:

Rosuvastatin and the insufferable odd couple heart failure and atrial fibrillation

Atrial fibrillation (AF) frequently complicates heart failure (HF) and vice versa and - when found together - for clinicians they form an insufferable odd couple. Once AF appears HF can worsen and stroke rate increases. Therefore prediction and prevention of AF may be desirable goals. Prevention of AF in HF patients using conventional antiarrhythmic drugs is associated with increased mortality. In these high risk patients primary prevention of AF using non-antiarrhythmic drugs such as ACE-inhibitors, angiotensin-receptor blockers and statins might be useful. The so-called upstream effects of these drugs prevent the atria from remodelling. This is important in HF patients since HF leads to stretch and fibrosis of the atria and atrial fibrillation. These notions are supported by experimental studies in which atrial fibrosis and atrial fibrillation was ameliorated by statin therapy. A recent meta-analysis incorporating 3 different primary prevention studies did not show a significant effect of statins with respect to incident AF. The ancillary study of GISSI-HF presented at the Clinical trial update at ESC can be added to this analysis. GISSI-HF found that rosuvastatin compared to placebo reduces - although non-significantly - the incidence of AF from 16 to roughly 14% in patients with HF. After adjustment there was however a statistically significant difference in favour of rosuvastatin but the anti-arrhythmic effect is not large and the question remains whether suppressing AF in HF patients is beneficial or only kills the messenger. Strictly speaking GISSI-HF was not a primary prevention trial since ~15% had had AF before and many more pts may have had asymptomatic AF, since detection of AF before inclusion was not very robustly performed. The GISSI-HF investigators took time to new onset of AF as an endpoint. Time to new onset AF is from technical viewpoint a very robust parameter. However, clinically the burden of AF or progression to persistent forms of AF is of more importance than one single event and in my mind - should be a focus of treatment of HF pts. The Kaplan-Meier survival curve shows step-ups at each visit since most of the incident AF was only detected at those time points suggesting that these patients were asymptomatic with their AF. This observation indicates that AF may not have had a large impact on the course of HF. Why did rosuvastatin not work as well as expected? The most important reason is that once AF emerges in the setting of HF the atria are already very fibrotic and strongly remodeled. Under those circumstances, a statin or other anti-fibrosis drug cannot be very effective anymore. This probably also holds for the patients included in GISSI-HF. Many GISSI-HF patients will have had HF for a long time providing the substrate for AF to develop. Unfortunately, as in all HF trials, the duration of HF is not mentioned in GISSI-HF. If available however, an interesting analysis might be to look

whether in pts with a short previous duration of HF rosuvastatin is more effective than placebo in preventing new onset AF and ameliorate the burden of AF. In summary, rosuvastatin is not extremely effective in preventing incident AF in patients with class II-IV CHF from any cause. There are still a few unanswered questions concerning the effects of statins in HF patients. First, it is important to know whether statins can reduce the progression and burden of AF? This is a question which might still be answerable from the GISSI-HF database. Secondly, can upstream statin therapy prevent AF in HF when started very early, i.e. before significant atrial fibrosis has occurred?. Finally, and most importantly, the question is whether all the efforts taken to uncouple AF from HF will eventually improve morbidity or mortality in these patients.

Characteristics of patients enrolled in the Predictors of Response to CRT (PROSPECT) trial: comparison of subgroups according to extent of LV reverse remodeling

Topics: Heart Failure (HF)

Session number: 1033-1034

Session title: Characteristics of patients enrolled in the Predictors of Response to CRT (PROSPECT) trial: comparison of subgroups according to extent of LV reverse remodeling

Authors: Van Bommel, Rutger - Linde, Cecilia

Presenter | see Discussant report
 Rutger van Bommel
 (The Netherlands)

List of Authors:

Rutger J. van Bommel, Jeroen J. Bax, William T. Abraham, Eugene S. Chung, Luis A. Pires, Luigi Tavazzi, Peter J. Zimetbaum, Bart Gerritse, Nina Kristiansen, Stefano Ghio

Abstract:

Introduction

PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy [CRT]) was the first large-scale, multicenter clinical trial that evaluated the performance of several echocardiographic measures of mechanical dyssynchrony to predict response to CRT. Although various markers of dyssynchrony contributed significantly to prediction of clinical outcome and LV reverse remodeling at 6 months follow-up, the sensitivity and specificity of these markers were modest. Though there is conflicting evidence about the prognostic value of LV reverse remodeling as a surrogate for patient outcome, it is routinely used for monitoring

CRT patients. A better understanding of which patient characteristics influence LV reverse remodeling is needed. Consequently, a detailed analysis of LV reverse remodeling at 6 months follow-up was performed in the patients enrolled in PROSPECT. Patients were divided according to the extent of LV reverse remodeling at 6 months follow-up and patients with super-response or negative-response were identified. Differences in clinical and echocardiographic characteristics between the groups were analyzed.

Methods

Patients were grouped according to the relative reduction in left ventricular end-systolic volume (LVESV) after 6 months of CRT. These subgroups were defined as follows: 1. super-responders: patients with a reduction in LVESV $\geq 30\%$, 2. responders: patients with a reduction in LVESV of 15% to 29%, 3. non-responders: patients with a reduction in LVESV ranging from 0% to 14% and, 4. negative-responders: patients with an increase in LVESV at 6 months follow-up.

Results

Two hundred and eighty-six patients with complete clinical assessment and complete, paired (baseline and 6 months follow-up) LVESV measurements were analyzed. Several baseline characteristics differed significantly between the 4 subgroups and were associated with either super-response or negative-response at 6 months follow-up (Table 1). Super-response was more frequently observed in: • Females • Patients with non ischemic heart failure • Patients with longer QRS duration • Patients with more baseline mechanical dyssynchrony Conversely, negative-response after CRT was more frequently observed in: • Patients in NYHA class IV • Patients with a history of VT Discussion Gender, etiology of heart failure, QRS duration, severity of heart failure, a history of ventricular tachycardia and presence of baseline mechanical dyssynchrony influence LV reverse remodeling after CRT and are associated with either super-response or negative-response at 6 months follow-up. The current findings help to better understand which characteristics influence the degree of LV reverse remodeling after CRT.

Table 1: Differences in baseline characteristics between super-responders (SUPER) responders (RESP), non-responders (NON) and negative responders (NEG).

	SUPER (n=108)	RESP (n=53)	NON (n=67)	NEG (n=58)	p-value
Age y	68 ± 10	67 ± 10	68 ± 11	68 ± 13	0.37
Gender, male, n (%)	63 (58)	43 (81)	49 (73)	47 (81)	0.0026
NYHA class IV, n (%)	1 (1)	2 (4)	3 (4)	5 (9)	0.016
Non ischemic etiology, n (%)	60 (56)	25 (47)	27 (40)	23 (40)	0.023
Diabetes, n (%)	27 (25)	16 (30)	22 (33)	16 (28)	0.52
History of AF, n (%)	21 (19)	11 (21)	10 (15)	11 (19)	0.71
History of VT, n (%)	19 (18)	13 (25)	25 (37)	23 (40)	0.0005
QRS duration, ms	166 ± 20	168 ± 26	163 ± 23	158 ± 24	0.033
LVEF, %	30 ± 9	27 ± 8	29 ± 11	29 ± 10	0.73
LVESV, mL	161 ± 88	196 ± 81	168 ± 90	167 ± 89	0.77
LVEDV, mL	223 ± 102	261 ± 93	230 ± 97	229 ± 100	0.83
LVT/RR, %	43 ± 9	43 ± 8	46 ± 8	45 ± 10	0.051
IVDM, ms	50 ± 35	47 ± 34	44 ± 38	25 ± 39	0.0002
Ts-(lateral-septal), ms	68 ± 44	50 ± 38	49 ± 38	44 ± 35	0.0022

AF: atrial fibrillation, IVMD: inter ventricular mechanical delay, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVFT/RR: left ventricular filling ratio, NYHA: New York Heart Association, Ts: time to peak systolic velocity, VT: ventricular tachycardia. Provided p-values are for trend between subgroups, Cochran-Mantel-Haenszel test for categorical variables and least squares regression for continuous variables.



Discussant see Presenter report
Cecilia Linde, FESC (Sweden)

Report: In this sub-study of PROSPECT Dr van Bommel et al focus on finding a combination of clinical and Doppler-echocardiography parameters to predict a response to CRT. This is a very relevant clinical question.

The present EHRA/ESC guidelines on cardiac pacing and CRT published in 2007 and the HFA/ESC guidelines on heart failure management updated 2008 state that patients in severe heart failure (NYHA III/IV) and left ventricular ejection fraction < 35% despite optimal heart failure medication are indicated for CRT with Class I A recommendation level of evidence A provided they have electrical dyssynchrony with a QRS width of > 120 ms. With these selection criteria 60-70% of patients respond to CRT in randomised controlled studies. But importantly 20% do not improve and another 20% even worsen by CRT. This is why the PROSPECT (PRedictors Of Response to CRT) studied the addition of mechanical dyssynchrony criteria to classical CRT selection criteria to enhance the response rate to CRT. The patients thus had to be in NYHA III/IV heart failure despite optimal medical therapy and have a LVEF < 35% sinus rhythm and QRS > 130 ms (the cutoff value used in the MIRACLE studies). This was the first large multi-center open clinical trial on this topic and with core-lab analysis of echo-data. The study published in *Circulation* (Chung et al *Cir* 2008;117:2608) assessed various M-mode or Tissue Doppler criteria for mechanical dyssynchrony for six-month improvement. Although some of these measures showed some promise either for clinical and echo-cardiography response no single criteria was sufficiently robust to firmly predict response to CRT above the expected response rate. The reason for this was to be found in the complex methodology with relatively low feasibility and reproducibility indicating that the methods need further refinement to be put into clinical practise. Whether a combination of these criteria would increase the response rate remain to be addressed. In this sub-study the authors looked at a spectra of clinically relevant baseline and echo parameters including some mechanical dyssynchrony criteria in their ability to

predict extent of reverse remodelling on the one hand and left ventricular reverse remodelling combined with clinical improvement after 6 months of treatment on the other hand. The study aimed to give some insights into prediction of a positive and negative response to CRT. Significant uni-variate predictors for presence and extent of reverse remodelling were non-ischemic aetiology, longer QRS at baseline or greater extent of mechanical dyssynchrony whereas significant predictors of getting worse were NYHA class IV and a history of ventricular tachycardia. For the combination of reverse remodelling and clinical improvement non-ischemic aetiology and extent of mechanical dyssynchrony were uni-variate predictors of response and history of ventricular tachycardia of getting worse during CRT.

My comments to this sub-study are the following:

1. The question asked is clinically relevant since we want more patients to respond to CRT and to avoid CRT to those who cannot be expected to respond or will deteriorate. The observed overall response rate to CRT in PROSPECT is as expected meaning that the studied patients are representative for CRT recipients to date. 2. The endpoints. Reverse remodelling although by definition a surrogate endpoint has been shown to be linked to mortality and morbidity in both drug studies and studies of CRT as recently shown in REVERSE (Linde et al *JACC* ;52:1834). Therefore the choice of this endpoint is clinically relevant. Overall there were 56.3% echo-responders (super-responders 37.8% and responders 18.5%). For the combination of clinical improvement using the percent improved by the clinical composite and decrease of LVESV by > 15% , 44.8% improved by both measures and 39.8 % by either of these and 15.4 % did not improve by any measure. It remains a bit unclear why the investigators chose two ways to assess reverse remodelling either super response (drop in LVESV of > 30%) and response (drop in LVESV of > 15%) esp. as the definition of a super response to CRT remains to be established. The added value of this division for the results appears limited. 3. The observation time. Super-response is most probably linked to time. In my opinion super-response means total restitution of left ventricular function. The observation time in this sub-study is limited to six months. It has been established from CARE-HF and most recently from the REVERSE studies (Daubert et al *JACC* 2009; in press) that reverse remodelling starts within the first 3 months of CRT but further evolves over at least a 18 months period. Therefore, the result of present study is limited by the relatively short observation time. 4. The methodology for establishing mechanical dyssynchrony is difficult and is linked to both inter and intra-observer variability. Paired data for LVESV were only available for 286 patients (67%) and the prevalence and extent of mechanical dyssynchrony varied. It is note-worthy that the simplest techniques such as interventricular mechanical delay (IVMD) were more prevalent and stronger uni-variate predictors than the more complex Tissue-Doppler techniques. For the baseline criteria this and randomised controlled CRT

studies such as MUSTIC and CARE-HF indicate that non-ischemic aetiology is linked to more extensive reverse remodelling. Some important factors likely to influence the response to CRT such as left ventricular lead position or presence and extent of left ventricular scar tissue were not analysed. 5. The number of patients studied and the uncontrolled study design. The number of patients in this study is relatively low and the study is open meaning that the results cannot be compared to the natural history of the heart failure in these patients. 6. The statistical analysis. Last but not least most of the baseline factors analysed are interrelated and only a multivariate analysis can establish their predictive value. This analysis remains to be done but is not likely to be conclusive with the low number of patients. Conclusion: This study addresses a relevant clinical problem but does not answer the question. In my opinion the only way to get any closer to finding predictors to CRT is to pool the data from already concluded large randomised trial and look for clinically robust parameters to predict who will benefit or not from CRT.

The risk of cardiovascular event for patients treated with clopidogrel or prasugrel in combination with a Proton Pump Inhibitor: Results from the TRITON-TIMI 38 Trial

Topics: Acute Coronary Syndromes (ACS)

Session number: 2694-2695

Session title: The risk of cardiovascular event for patients treated with clopidogrel or prasugrel in combination with a Proton Pump Inhibitor: Results from the TRITON-TIMI 38 Trial

Authors: O'Donoghue, Michelle - Huber, Kurt



Presenter | see Discussant report
 Michelle O'Donoghue
 (United States of America)

List of Authors:

Michelle L. O'Donoghue, Stephen D. Wiviott, Elliott M. Antman, Sabina A. Murphy, Charles F. Contant, Eric R. Bates, Yoseph Rozenman, Carolyn H. McCabe, Jessica L. Mega, Marc S. Sabatine, Eugene Braunwald

Abstract:

Background:

Prasugrel significantly reduces cardiovascular events as compared with clopidogrel in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI), but with an increased risk of bleeding. Proton pump inhibitors (PPI) are often prescribed to patients in combination with thienopyridines to help reduce the risk of gas-

trointestinal bleeding. Some data suggest that many PPIs may reduce the antiplatelet effects of clopidogrel by inhibiting CYP2C19 and thus the conversion of clopidogrel to its active metabolite. The clinical implications of co-administration of a PPI with either clopidogrel or prasugrel remain undefined.

Methods:

The TRITON-TIMI 38 trial randomized 13,608 subjects with ACS and planned PCI to prasugrel or clopidogrel, in addition to standard therapy. The primary endpoint of the trial was cardiovascular death, MI or stroke. The decision to treat with a proton pump inhibitor was left to the discretion of the treating physician and was captured on the case-report forms. A multivariable Cox proportional hazards model was used to evaluate the association between use of a PPI at randomization and the risk of long-term clinical outcomes. The multivariable model included potential confounders and a propensity score constructed with 15 variables associated with use of a PPI. Further sensitivity analyses were performed to evaluate the association between use of a PPI at different timepoints during follow-up, different types of PPIs, and the risk of short- or long-term cardiovascular events.

Results:

Of the 13,608 subjects enrolled in TRITON-TIMI 38, 33% of subjects were being treated with a PPI at randomization. For patients randomized to clopidogrel, the rate of the primary endpoint through long-term follow-up was 11.8% in subjects on a PPI and 12.2% in subjects not on a PPI (HR 0.98, 95% CI 0.84-1.14, P=0.80). For patients randomized to prasugrel, the rate of the primary endpoint was 10.2% in subjects on a PPI and 9.7% in subjects not on a PPI (HR 1.05, 95% CI 0.89-1.23, P=0.53). After adjusting for known confounders and the propensity to treat with a PPI, there remained no significant association between the use of a PPI and the risk of the primary endpoint, both for patients treated with clopidogrel (adjusted HR 0.94, 95% CI 0.80-1.11) or for those treated with prasugrel (adjusted HR 1.00, 95% CI 0.84-1.20). Similarly, the use of a PPI was not associated with an increased risk of MI, stent thrombosis, or urgent revascularization, or a decreased risk of bleeding, for patients treated with either clopidogrel or prasugrel (Table). Sensitivity analyses demonstrated consistency of the results based on use of PPI at different timepoints during follow-up, different types of PPIs, and varying durations of follow-up.

	Clopidogrel (n=6795)			Prasugrel (n=6813)		
	Treated with a PPI (n=2257)	Not treated with a PPI (n=4538)	Adjusted HR (95% CI)	Treated with a PPI (n=2272)	Not treated with a PPI (n=4541)	Adjusted HR (95% CI)
CV death, MI or stroke	11.8%	12.2%	0.94 (0.80-1.11)	10.2%	9.7%	1.00 (0.84-1.20)
Myocardial infarction	9.5%	9.8%	0.96	7.7%	7.3%	1.02 (0.84-1.25)
Stent thrombosis (ARC definite or probable)	2.4%	2.3%	1.00 (0.75-1.35)	1.1%	1.1%	1.03
TIMI major bleeding	2.4%	1.6%	1.20 (0.80-1.79)	2.5%	2.4%	0.97 (0.67-1.39)
Net clinical outcome (death, MI, stroke or TIMI major non-CABG bleeding)	13.9%	13.8%	0.96 (0.83-1.12)	12.6%	12.1%	0.99 (0.85-1.17)

Conclusion:

In a large population of subjects treated with clopidogrel or prasugrel, the use of a PPI was not associated with an increased risk of cardiovascular events.



Discussant see Presenter report
Kurt Huber, FESC (Austria)

Report:

Background:

In this interesting study the authors investigated by retrospective analysis of patients of the TRITON TIMI-38 trial whether the use of proton pump inhibitors (PPI) negatively influences clinical outcome compared with non-use. Controversial data of clinical outcome from other authors as well as studies, which demonstrated a reduced action of clopidogrel on in vitro testing of platelet function when PPIs, especially omeprazole, were used, were the background of the investigation. Of special interest was the opportunity to test the potential influence of PPIs on prasugrel, a new thienopyridine, which showed favorable effects over clopidogrel in the TRITON TIMI-38 trial.

Methods and Statistics:

The TRITON-TIMI 38 trial randomized 13,608 subjects with ACS and planned PCI to prasugrel or clopidogrel, in addition to standard therapy, of which 4,538 (20%) were being treated with a PPI at randomization. Use of a PPI was on discretion of the treating physician and not randomized. A multivariable Cox proportional hazards model, which included potential confounders and a propensity score constructed with 15 variables associated with use of a PPI, was used to evaluate the association between use of a PPI at randomization and the risk of long-term clinical outcomes.

Results:

After adjusting for known confounders and the propensity to treat with a PPI, there remained no significant association between the use of a PPI and the risk of the primary endpoint, either for patients treated with clopidogrel (adjusted HR 0.94, 95% CI 0.78-1.13) or for those treated with prasugrel (adjusted HR 0.94, 95% CI 0.77-1.16).

Comments:

In opposite to several other investigations with higher patient numbers, in this population of subjects treated with clopidogrel or prasugrel, the use of a PPI was not associated with an increased risk of cardiovascular events. What are the differences of TRITON TIMI-38 to other investigations, which make the results more reliable for clinical practice? Based on the fact that patients have

not been randomized to receive or not to receive a PPI in all studies published so far, different inclusion bias might have triggered the different clinical outcomes. In addition, the current data come from a prospective randomized trial with a well-defined study population. This might be different to the study populations of other trials and registries including patients with higher age and more co-morbidities - which is frequently the reason to use PPIs - and therefore at higher risk for clinical events. Differences in outcome might also be explained by different statistical approaches. Also the consistent use PPIs during dual antiplatelet therapy might have impact on clinical outcome. It would be of interest to know whether the authors have performed in vitro platelet function testing and whether the test results are related with the clinical outcome. Unfortunately, also the TRITON TIMI-38 substudy on the impact of use or non-use of PPIs on clinical outcome in clopidogrel or prasugrel-treated patients does not fully answer the still open questions. Only a prospective randomized trial of PPI use will be capable of establishing the safety of PPIs in combination with thienopyridines.

Effect of rosiglitazone on coronary events in the RECORD study

Topics: Cardiovascular Disease Prevention - Risk Assessment and Management

Session number: 2796-2697

Session title: Effect of rosiglitazone on coronary events in the RECORD study

Authors: McMurray, John - Charbonnel, Bernard



Presenter | see Discussant report
John McMurray, FESC
(United Kingdom)

List of Authors:

J McMurray, M Komajda, H Beck-Nielsen, R Gomis, M Hanefeld, S Pocock, P Curtis, N Jones & P Home on behalf of the RECORD Committees and Investigators

Abstract:

Concern had been raised that treatment with rosiglitazone might increase the risk of myocardial infarction in patients with diabetes on the basis of a meta-analysis of small, short-term, trials that had methodological limitations (Nissen and Wolski N Engl J Med 2007; 356: 2457-71) . The present analyses describe the occurrence of prospectively identified coronary events occurring during a large-scale, long-term (average follow-up 5.5 years), randomized trial comparing treatment with rosiglitazone added to back-

ground metformin or sulfonylurea monotherapy (n=2220) with combination metformin plus sulfonylurea treatment (n=2227) in patients with type II diabetes mellitus – the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study. All events were adjudicated by an endpoint committee blinded to treatment allocation using pre-specified definitions. The composite outcome of fatal and non-fatal myocardial infarction (a pre-defined secondary endpoint) was reported in the primary paper (Home et al Lancet 2009; 373; 2125-35). The present report describes i) subsequent acute coronary events and mortality in these patients ii) a range of post hoc composite coronary outcomes, analysed as time to first event and iii) total coronary events, taking account of recurrent events (i.e. that patients can experience more than one event). The additional coronary composites analysed included a) Any acute coronary syndrome (fatal MI, sudden death, hospitalization for cardiac arrest, hospitalization for acute MI or hospitalization for unstable angina) b) Any acute coronary syndrome (ACS) or other angina (above plus patients with an “other” cardiovascular hospitalization attributed to angina pectoris) and c) Any ACS, other angina or coronary revascularization (above plus either percutaneous coronary intervention or coronary artery bypass surgery). The attached slides show these outcomes. Among the 60 survivors of a first MI in the rosiglitazone group, there were 7 recurrent MIs and 3 cases of unstable angina pectoris. There were 11 deaths (of which 7 were cardiovascular). Among the 52 survivors of a first MI in the control group (metformin plus a sulfonylurea), there were 11 recurrent MIs and 2 cases of angina pectoris. There were 12 deaths (of which 10 were cardiovascular). The expanded coronary composites showed similar event rates in both treatment groups. The total number of coronary events were similar in the two groups – for the broadest composite, 127 patients in the rosiglitazone group experienced 221 events compared to 128 patients (230 events) in the control group.

Discussant see Presenter report
Bernard Charbonnel, FESC (France)

Effect of ivabradine on cardiovascular outcomes in patients with stable CAD and LV dysfunction with limiting angina: a subgroup analysis of the BEAUTIFUL trial

Topics: Chronic Ischaemic Heart Disease (IHD)

Session number: 2698-2699

Session title: Effect of ivabradine on cardiovascular outcomes in patients with stable CAD and LV dysfunction

with limiting angina: a subgroup analysis of the BEAUTIFUL trial

Authors: Ferrari, Roberto - Heusch, Gerd



Presenter | see Discussant report
Roberto Ferrari, FESC (Italy)



Discussant see Presenter report
Gerd Heusch, FESC (Germany)

Report:

The BEAUTIFUL investigators present a retrospective, subgroup analysis in 13.8% of the original patient population who had limiting symptomatic angina – as characterized by pain, fatigue, palpitations or dyspnoea – at baseline. The essential conclusions from the original BEAUTIFUL study were largely confirmed and further emphasized: now with a just borderline-significant reduction in the composite endpoint, ivabradine had no effect on mortality and hospitalization for heart failure, but significantly reduced the hospitalization for myocardial infarction and coronary revascularization, and this reduction was more pronounced in patients with heart rate above 70/min than in the entire population with limiting angina; the placebo-corrected heart rate reduction was only 4/min and 7/min in the entire population with limiting angina and in those with limiting angina and a heart rate above 70/min, respectively.

The investigators appropriately acknowledge the limitations of their retrospective approach to analyze a subgroup of a trial which was entirely negative in its primary endpoint and advocate their analysis as hypothesis-generating and in need of large-scale prospective testing. Unfortunately, they say not precisely which hypothesis they generate from their subgroup analysis, possibly that ivabradine provides greater protection from ischemia in patients with coronary artery disease and limiting angina than in those without angina; to test such hypothesis would require a huge trial. Somewhat surprisingly, the investigators fail to critically discuss their choice of limiting angina as the entry criterion for their subgroup analysis. While they expand in detail on the impact of angina on prognosis, exactly this is obviously not true for the BEAUTIFUL patients with limiting angina who had a mortality of 10.0% with placebo as compared to 10.1% in the entire BEAUTIFUL population with placebo. The reasons for the lack of impact of angina on prognosis in this study population remain unclear: the excellent anti-anginal background medication or potential cardioprotective phenomena related to

repeated episodes of reversible ischemia/reperfusion, such as ischemic preconditioning or – in conjunction with left ventricular dysfunction – myocardial hibernation, might have offset the otherwise adverse effects of angina on prognosis. Notwithstanding the above limitations, the current subgroup analysis in patients with limiting angina confirms the original BEAUTIFUL trial, in that ivabradine protects from ischemia and not from heart failure and that protection is more pronounced in patients with heart rate above 70/min. However, the placebo-corrected heart rate reduction by no more than 7/min, respectively, with ivabradine strikes me as modest and difficult to reconcile with the profound protection. Also difficult to reconcile are the facts, that heart rate above 70/min was a stronger discriminator for heart failure than ischemia outcome, but then there was no protection from heart failure but only from ischemia endpoints with heart rate reduction. So is there protection from ischemia by ivabradine beyond that by heart rate reduction? Experimental studies in pigs clearly revealed a significant reduction in infarct size with ivabradine, not only when given before ischemia but also when given just at reperfusion, and such infarct size reduction was largely preserved when heart rate reduction was offset by atrial pacing. This pleiotropic protective action of ivabradine beyond its bradycardic effect puts ivabradine into the context of cardioprotection and its signal transduction, notably into the context of postconditioning since ivabradine is still protective when given just at reperfusion. The mechanism(s) underlying the pleiotropic protection by ivabradine are largely unclear; attenuation of damage by reactive oxygen species and reduced sodium influx through the I_f current with secondary reduction of sodium – calcium exchange and ultimate reduction in calcium overload have been suggested. Experimental studies, e.g. with ivabradine on top of sodium-calcium exchange blockade or anti-oxidant regimes, are required to elucidate the potential pleiotropic protective mechanism of ivabradine. Clinical studies are required to confirm the experimental data on protection by ivabradine against reperfusion injury; a similar study design as in the most recent trial on cyclosporine A in patients with acute myocardial infarction would be most useful. A detailed Editorial with references is available on the Eur Heart J website as of today.

Randomized evidence on Rosuvastatin for primary prevention in individuals 70 years of age or older. JUPITER

Topics: Cardiovascular Disease Prevention - Risk Assessment and Management

Session number: 2700-2701

Session title: Randomized evidence on Rosuvastatin for primary prevention in individuals 70 years of age or older. JUPITER

Authors: Glynn, Robert - Steg, Philippe Gabriel



Presenter | see Discussant report
Robert Glynn,
(United States of America)

List of Authors:

Robert J Glynn and Paul M Ridker on behalf of the JUPITER Trial Study Group

Abstract:

Relationships of cholesterol levels with cardiovascular risk weaken with advancing age, and use of statins for primary prevention in older people remains controversial.

Among the 17802 apparently healthy men and women randomized in the JUPITER trial, 5695 were initially age 70 years or older. The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0) on the basis of convincing evidence of efficacy with respect to the combined primary end point. We present here the observed effects of rosuvastatin in participants age 70 years or older, based on intention-to-treat analyses, for the composite primary end point and the pre-specified secondary end points of total mortality, venous thromboembolism, and incident diabetes.

The 32% of participants in the JUPITER trial who were aged 70 years or older accrued 49% (N=194) of the 393 confirmed primary end points. The rates of the primary end point in this age group were 1.22 and 1.99 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio 0.61; [95% CI, 0.46 to 0.82]; $P < 0.001$). Corresponding rates of secondary end points in this age group were 1.63 and 2.04 for any death (hazard ratio 0.80; [95% CI, 0.62 to 1.04]; $P = 0.090$), 0.24 and 0.41 for venous thromboembolism (hazard ratio 0.58; [95% CI, 0.31 to 1.11] $P = 0.096$), and 1.20 and 0.98 for diabetes (hazard ratio 1.21; [95% CI, 0.86 to 1.71]; $P = 0.27$). Thus, relative effects observed in older participants were quite similar to those reported for the overall trial.

However, because absolute risks were substantially higher in this age group, the estimated number needed to treat (NNT) for 5 years to prevent 1 primary end point was 19, compared with the estimated NNT of 25 for the overall trial.



Discussant see Presenter report
Philippe Gabriel Steg, FESC (France)

International impact of atherothrombotic vascular disease and events: 3-year data from the REACH Registry

Topics: Cardiovascular Disease Prevention - Risk Assessment and Management

Session number: 2702-2703

Session title: International impact of atherothrombotic vascular disease and events: 3-year data from the REACH Registry

Authors: Alberts, Mark - Danchin, Nicolas



Presenter | see Discussant report
Mark Alberts,
(United States of America)

List of Authors:

Mark J Alberts, Ph Gabriel Steg, Deepak L Bhatt, Jean-Louis Mas, E Magnus Ohman, Alan T Hirsch, Joachim Röther

Abstract:

Background:

Atherothrombotic vascular disease is the leading cause of morbidity and mortality throughout the world. Accurate, contemporary and international data on the outcomes of outpatients with vascular disease are important for planning medical interventions and formulating effective public health policies, but are lacking.

Methods:

We used data from the ongoing REACH Registry, an observational study of outpatients with atherothrombosis (established coronary artery disease [CAD], cerebrovascular disease [CVD], or peripheral arterial disease [PAD]), or with at least three atherothrombotic risk factors from 44 countries. The aim was to determine outcome events after 3 years of follow-up. All patients were seen annually (every 6 months in the United States) to determine the occurrence of events such as myocardial infarction (MI), stroke, cardiovascular (CV) death, or hospitalization for vascular reasons.

Results:

As of March 2009, 3-year outcomes were available for 38 909 patients (81% of those eligible for follow-up), including 32 247 with symptomatic disease. Among the symptomatic patients, 92% were taking antithrombotic agents and 76% were on lipid-lowering therapy. For MI/stroke/CV death, the 1- and 3-year event rates for all patients were 4.2% and 11.0%, respectively. Event rates (MI/stroke/CV death) were significantly higher for patients with symptomatic disease vs those with risk factors only at 1 year (4.7% vs 2.3%, $p<0.001$) and at 3 years (12.0% vs 6.2%, $p<0.001$). The 1- and 3-year rates of MI/stroke/CV death/hospitalization were 14.4% and 28.4%, respectively, for patients with symptomatic disease. Hospitalization for a vascular event other than MI/stroke/CV death was common at 3 years, with rates

of 19.0% for the entire cohort, 33.8% for PAD, and 23.0% for CAD. For patients with symptomatic vascular disease in one vascular bed vs multiple vascular beds, the 3-year event rates for MI/stroke/CV death/hospitalization were 25.5% vs 40.5% ($p<0.001$).

Conclusions:

Despite contemporary therapy, outpatients with symptomatic atherothrombotic vascular disease still experience high rates of recurrent events and hospitalizations. This patient population has a very high utilization rate of medical resources and should be targeted for improved disease-prevention efforts.



Discussant see Presenter report
Nicolas Danchin, FESC (France)

Nonfasting cholesterol and triglycerides, myocardial infarction, and early death. Copenhagen City Heart

Topics: Acute Coronary Syndromes (ACS)

Session number: 2704-2705

Session title: Nonfasting cholesterol and triglycerides, myocardial infarction, and early death. Copenhagen City Heart

Authors: Nordestgaard, Borge - Fuster, Valentin



Presenter | see Discussant report
Borge Nordestgaard, (Denmark)

List of Authors:

Anne Langsted, MD, Jacob J Freiberg, MD, Anne Tybjærg-Hansen, MD, DMSc, Peter Schnohr, MD, DMSc, Gorm B Jensen, MD, DMSc, and Børge G Nordestgaard MD, DMSc.

Abstract:

Context:

Current guidelines recommend identification and treatment of elevated cholesterol levels, but not of nonfasting triglycerides.

Objective:

We compared the ability of cholesterol and triglycerides measured nonfasting at random to predict risk of myocardial infarction and total mortality.

Design, setting, and participants:

We followed 7581 women and 6391 men aged 20 to

93 years from the Danish general population for 31 years. Among women, 768 developed myocardial infarction and 4398 died; corresponding numbers in men were 1151 and 4416. Follow-up was 100% complete. Main outcome measures: Plasma cholesterol and triglycerides measured nonfasting at random, lipoproteins, traditional cardiovascular risk factors and end-points. Results: Elevated nonfasting total cholesterol mainly marked elevated low density lipoprotein cholesterol levels while elevated nonfasting triglyceride levels mainly marked elevated remnant lipoprotein cholesterol levels. Compared to women with cholesterol <5mmol/L, multivariate adjusted hazard ratios for myocardial infarction ranged from 1.3(95%CI 0.9-1.8) for cholesterol of 5-5.99 mmol/L to 2.5 (1.6-4.0) for cholesterol =9mmol/L (trend $p<0.0001$), while compared with women with nonfasting triglycerides <1 mmol/L, hazard ratios ranged from 1.5 (1.2-1.8) for triglycerides of 1-1.99 mmol/L to 4.2(2.5-7.2) for triglycerides =5mmol/L ($p<0.0001$). In men, corresponding hazard ratios ranged from 1.2 (1.0-1.5) to 5.3 (3.6-8.0) for cholesterol ($p<0.0001$), and from 1.3(1.0-1.6) to 2.1 (1.5-2.8) for triglycerides ($p<0.0001$). Increasing cholesterol levels did not consistently associate with total mortality in women (trend $p=0.39$) or men ($p=0.02$). In contrast, compared with women with triglycerides <1 mmol/L, multivariate adjusted hazard ratios for total mortality ranged from 1.1 (1.0-1.2) for triglycerides of 1-1.99 mmol/L to 2.0(1.5-2.9) for triglycerides =5mmol/L (trend $p<0.0001$); corresponding hazard ratios in men ranged from 1.1(1.0-1.2) to 1.5(1.2-1.7) ($p<0.0001$).

Conclusion:

Stepwise increasing levels of both nonfasting cholesterol and nonfasting triglycerides associate with stepwise increasing risk of myocardial infarction; however, only increasing levels of nonfasting triglycerides consistently associate with total mortality.



Discussant see Presenter report
Valentin Fuster, FESC
(United States of America)

Clinical outcome after thrombectomy or standard angioplasty in patients with ST elevation myocardial infarction: individual patient-data pooled analysis of 11 randomized trials. ATTEMPT

Topics: Acute Coronary Syndromes (ACS)

Session number: 5021-5022

Session title: Clinical outcome after thrombectomy or standard angioplasty in patients with ST elevation myocardial infarction: individual patient-data pooled analysis of 11 randomized trials. ATTEMPT

Authors: Burzotta, Francesco - Eeckhout, Eric



Presenter | see Discussant report
Francesco Burzotta, FESC (Italy)

List of Authors:

Francesco Burzotta, Maria De Vita (Co-first investigator), Youlan Gu, Takaaki Isshiki, Thierry Lefèvre, Anne Kaltoft, Dariusz Dudek, Gennaro Sardella, Pedro Silva Orrego, David Antonucci, Leonardo De Luca, Giuseppe GL Biondi-Zoccai, Filippo Crea, Felix Zijlstra.

Abstract:

Background:

Trials on thrombectomy in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) have shown favourable impact on myocardial reperfusion. However, no published study was adequately powered to assess the impact of thrombectomy on long term clinical outcome. Thus, we conducted a collaborative individual patient-data pooled analysis aimed to assess the long-term clinical outcome in STEMI patients randomized to percutaneous coronary intervention (PCI) with or without thrombectomy (study acronym: ATTEMPT, Number of registration in clinical-trial.org website: NCT00766740).

Methods

Principal investigators of randomized trials comparing thrombectomy with standard PCI in patients with STEMI were contacted. Agreeing investigators constituted the ATTEMPT Investigators (SEE APPENDIX) and provided a series of key pre-PCI data as well as the longest available clinical outcome of the patients enrolled in the corresponding trial. Primary end-point was all-cause mortality during the follow-up. Secondary end-points were major adverse cardiac events (MACE: all-cause death and/or target lesion/vessel revascularization (TLR/TVR) and/or myocardial infarction (MI)), MI, all-cause death + MI and TLR/TVR. Moreover, the effect of thrombectomy on clinical outcome was assessed in a series of predefined patients' subgroups.

Findings

Individual data of 2686 patients enrolled in 11 trials entered the pooled analysis. Clinical follow-up was available in 2674 (99.6%) patients at a median of 365 days.

- Primary end-point

Kaplan-Meier analysis at the longest available follow-up showed that allocation to thrombectomy was associated with reduced all-cause mortality (log-rank $p=0.049$) (figure 1).

- Secondary end-points

Kaplan-Meier analyses at the longest follow-up available, either crude or stratified by study (which provided similar results for direction and magnitude of

statistical significance), showed that allocation to thrombectomy was associated with significantly fewer MACE (log-rank $p=0.011$) and death+MI (log-rank $p=0.015$), but non-significant differences in MI (log-rank $p=0.126$) or in TLR/TVR (log-rank $p=0.126$).

Subgroups analysis

- Type of thrombectomy device The ATTEMPT study population was divided in two groups considering the type of thrombectomy device used: manual thrombectomy group (1815 patients enrolled in trials with use of Diver CE, Pronto and Export catheters) and non-manual thrombectomy group (871 patients enrolled in trials with use of X-Sizer, Angiojet, Rescue and TVAC devices). In the manual thrombectomy group Kaplan-Meier analyses at the longest follow-up available showed that allocation to thrombectomy was associated to significantly fewer deaths (log-rank $p=0.011$; estimated number of patients needed to treat to save 1 life: 34) while in the non-manual thrombectomy group the allocation to thrombectomy was associated to similar mortality compared to standard PCI (log-rank $p=0.481$) (figure 2).

- Clinical and angiographic subgroups

There was no difference in mortality when splitting the study population according to the presence or absence of diabetes, to shorter, intermediate or longer time-to-reperfusion, to type of culprit artery (left anterior descending or circumflex artery or right coronary artery) and to pre-PCI TIMI flow (0-1 or 2-3). Conversely, a significant benefit of thrombectomy in terms of survival was present in the subgroup of patients treated with IIB/IIIa inhibitors (1787 patients; log-rank $p=0.045$; HR 0.61, 95%CI 0.38-0.90) and not in those not receiving this drugs (899 patients; log-rank $p=0.843$; HR 0.93, 95%CI 0.48-1.80). Interestingly, in a post-hoc analysis stratified according to thrombectomy use and IIB/IIIa inhibitors administration, patients treated by both thrombectomy and IIB/IIIa inhibitors had the lower mortality rate, those who had none of these treatments had the higher mortality rate, patients receiving only one of these therapies exhibiting intermediate outcome (figure 3)

Interpretation

The present large pooled analysis of randomized trials suggests that thrombectomy, when performed by manual thrombus-aspirating catheters, significantly improves survival in patients with STEMI undergoing mechanical reperfusion and that its effect may be additional to that of IIB/IIIa inhibitors.



Discussant see Presenter report
Eric Eeckhout, FESC (Switzerland)

Report:

Primary percutaneous coronary intervention (PCI) has received the highest level of recommendation and evidence for practice by our 2008 Society Guidelines on the management of patients with ST-segment elevation myocardial infarction. At present, primary PCI is a daily activity in most catheterization laboratories around the world. Over time, primary PCI practice has taught us that the classical TIMI flow is not an adequate marker to judge the quality of reperfusion at the level of the myocardium. The no-reflow phenomenon has been defined as the inability to restore perfusion at tissue level despite the absence of epicardial mechanical obstruction. No-reflow is particularly frequent during primary PCI (up to 40% of cases) and is partially explained by distal embolization of thrombus from the instrumented infarct-related artery. No-reflow during primary PCI has a prognostic impact and its prevention is a major objective during primary PCI. From a technical point of view, manual thrombus aspiration prior to stenting has emerged as a simple and very effective tool to prevent no-reflow. Indeed, this has been demonstrated by the large (single-center) TAPAS trial which further showed survival benefit at 1 year follow-up. During the clinical trial update III, Burzotta et al. present a meta-analysis of randomized controlled trials on thrombectomy during primary PCI (ATTEMPT). This meta-analysis was able to include 11 out of 17 studies identified after a careful MEDLINE search. A total of 2686 individual patient data were available for a pooled analysis. The primary end point was all cause mortality and a subgroup analysis was predefined on the type of thrombectomy technique and the administration of IIB/IIIa antagonists. The investigators were requested to provide the longest follow-up available. The main conclusions of the ATTEMPT study are the following: systematic thrombectomy during primary PCI improves survival at 1 year; survival benefit is observed after manual thrombectomy only; an additional benefit is obtained in patients treated with IIB/IIIa antagonists. What are the positive features of this study? This is a pooled analysis of individual patient data on a relevant and practical question. The analysis was performed by individual investigators without financial support. In order to check for heterogeneity, internal validity and publication bias a complex statistical analysis was performed. Finally, the follow-up of each study was updated and significantly extended. As usual, a meta-analysis raises a few points of concern. The role of the secondary end points is unclear in view of such a hard positive end point as mortality. They are particularly vulnerable to error in interpretation. Furthermore, the predefined subgroups (other than thrombectomy type and the use of IIB/IIIa antagonists) are underpowered to make any reasonable conclusions. Finally, the absence of 6 out of 17 trials is certainly the major limitation of ATTEMPT. The majority involves non manual thrombectomy trials and, even if these studies have revealed negative results, the global analysis imbalances further in favour of manual thrombectomy.

Still, these limitations do not counterweight the merit of the ATTEMPT study. Manual thrombectomy, should be standard practice during primary PCI.

Optimal revascularization strategy in patients with three-vessel disease and/or left main disease: The 2 year outcomes of the SYNTAX Trial

Topics: Acute Coronary Syndromes (ACS)

Session number: 5023-5024

Session title: Optimal revascularization strategy in patients with three-vessel disease and/or left main disease: The 2 year outcomes of the SYNTAX Trial

Authors: Kappetein A Pieter - Antunes Manuel J



Presenter | see Discussant report
A Pieter Kappetein, FESC
(Netherlands)

List of Authors:

A. Pieter Kappetein, MD PhD; David R. Holmes, MD; Friedrich W. Mohr, MD PhD; Patrick W. Serruys, MD PhD; Elisabeth Stähle, MD; Ted E. Feldman, MD; Michael J. Mack, MD; Antonio Colombo, MD; Keith D. Dawkins, MD; Marie-Claude Morice, MD

Abstract:

Purpose:

The SYNTAX trial was designed to compare percutaneous coronary intervention (PCI) with coronary artery bypass surgery (CABG) for the treatment of de novo three-vessel (3VD) and/or left main coronary disease (LM).

Methods:

SYNTAX is a prospective, multinational, randomized clinical trial with parallel nested registries. Consecutive patients with de novo 3VD and/or LM disease were screened by a Heart Team (cardiac surgeon and interventional cardiologist). If determined to be amenable for equivalent revascularization with both treatments, they were randomized to PCI or CABG, stratified by LM disease and diabetes. If a patient was suitable for only 1 treatment option, they were entered into the PCI registry for CABG-ineligible patients or CABG registry for PCI-ineligible patients.

Results:

A total of 1,800 patients were randomized at 85 sites and 198 patients were enrolled in the PCI registry and 1,077 in the CABG registry. The primary endpoint of SYNTAX, 12-month binary MACCE (major adverse cardiac and cerebrovascular events: all-cause death, stroke, MI, repeat revascularization), was significantly higher in

the PCI arm (12.4% CABG vs 17.8%) due, in large part, to increased repeat revascularization (CABG 5.9% vs PCI 13.5%).

Two-year outcomes are shown in the Table. MACCE (analyzed in a time-to-event manner) was significantly increased in PCI patients (CABG 16.3% vs PCI 23.4%; $P=0.0002$); however, the composite safety endpoint of death/stroke/MI was comparable between the 2 groups (CABG 9.6% vs PCI 10.8%; $P=0.44$). Similar to outcomes after the first year of follow-up, the increase in MACCE at 2 years was mainly attributable to an increased rate of repeat revascularization in PCI-treated patients (CABG 8.6% vs PCI 17.4%; $P<0.0001$); most repeat revascularization occurred within the first year. The rate of MI was significantly increased in PCI patients (CABG 3.3% vs PCI 5.9%; $P=0.01$), whereas stroke remained significantly higher in CABG patients (CABG 2.8% vs PCI 1.4%; $P=0.03$) after 2 years of follow-up. In the LM subgroup, MACCE rates were comparable between CABG and PCI-treated patients (CABG 19.3% vs PCI 22.9%; $P=0.27$). In contrast, in those patients with 3VD the difference in MACCE favored CABG (CABG 14.4% vs PCI 23.8%; $P=0.0001$). The impact of lesion complexity on 2-year clinical outcomes was estimated by examining patient outcomes relative to SYNTAX Score tercile. The rates of MACCE were not significantly different between patients with low SYNTAX Scores treated with either PCI or CABG (CABG 17.4% vs PCI 19.4%, $P=0.63$). In patients with intermediate SYNTAX Scores, there was a trend towards increased MACCE with PCI (CABG 16.4% vs PCI 22.8%, $P=0.06$). In the most complex patients (SYNTAX Scores ≥ 33), MACCE was significantly increased in patients treated with PCI (CABG 15.4% vs PCI 28.2%; $P=0.0001$).

2-Year Adverse Event Rates (Times-to-event rates)

	CABG	PCI	Stroke	CABG	PCI
MACCE	16.3	23.4		2.8	1.4*
Death/Stroke Myo-					
cardial infarction	9.6	10.8	MI	3.3	5.9*
Death, all-cause	4.9	6.2	Repeat	8.6	17.4*

* $P<0.05$

Conclusions:

The 2-year SYNTAX results suggest that CABG remains the standard of care for patients with complex 3VD and/or LM (high SYNTAX Scores) as CABG demonstrated lower MACCE rates compared to PCI at 2 years. However, PCI may be an acceptable alternative revascularization method to CABG when treating patients with less complex (low or intermediate SYNTAX Score) 3VD and/or LM disease. The SYNTAX patients will be followed for 5 years.



Discussant see Presenter report
Manuel J Antunes, FESC (Portugal)

Report:

The Syntax trial, run simultaneously in Europe and in the USA, has a randomized arm, with 1,800 patients, and a registry arm, with 1,275 patients. Randomization was made in each centre after Surgeons and Interventional Cardiologists agreed that the patient was suitable for both revascularization procedures, a major difference to previous randomized studies. When the first year follow-up was published in March 2009, it was stated that "CABG remains the standard care for patients with 3-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end-point of major adverse cardiac or cerebrovascular events at 1 year". It appears to have had no impact on practice in most interventional cardiology laboratories. It is a half-full-half-empty glass like situation. Each party interpreted the results its own way. CRT-online stated "Landmark Syntax trial reports comparable safety outcomes for complex patients treated with Taxus Express2 stents or bypass surgery". By contrast, a press release by the Society of Thoracic Surgeons stated that "Syntax trial results confirm better outcomes using bypass surgery for complex coronary disease". The 2-year follow-up now presented to us confirms all the results and trends shown by the 1-year report. The differences that were statistically different remain so and the differences which were not significant continue the trends towards significance which, it all appears to indicate, will reach with time. That includes all-cause death and myocardial infarction, which are higher in PCI than in CABG, while the incidence of CVA, higher in the first year after CABG, appears to have evened out in the second year. Besides, the need for re-revascularization and the incidence of MACE (major adverse cardiac events) clearly favour surgery. Hence, it is difficult to agree with the conclusions now presented, which, in my view, intend to soften the clear disadvantages of PCI in this complex coronary disease, which will, almost certainly, be quite clear in the 5-year follow-up, the next step of the trial. One good thing, however, has resulted from this trial: the development of the Syntax score whose calculator is now available online for download, which is a welcome tool for evaluation of the complexity of coronary artery disease, to permit meaningful comparisons between the results of different series of revascularization.

Fractional flow reserve versus angiography for guiding PCI

Topics: Acute Coronary Syndromes (ACS)

Session number: 5025-5026

Session title: Fractional flow reserve versus angiography for guiding pci - 2 year outcome

Authors: Pijls, Nico HJ - Luescher, Thomas Felix



Presenter | see Discussant report
Nico HJ Pijls, FESC (Netherlands)

List of Authors:

Nico H.J. Pijls, Pim A.L. Tonino, Bernard De Bruyne, Volker Klauss, Ganesh Manoharan, Thomas Engstrom, Peter N. Ver Lee, Philip A. MacCarthy, Keith G. Oldroyd, William F. Fearon

Abstract:

Introduction:

In patients with multivessel coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) it is unclear whether routine measurement of fractional flow reserve (FFR) in addition to angiography improves outcome.

Methods:

At 20 U.S. and European medical centers, 1005 patients with multivessel CAD were randomized to PCI with drug-eluting stents (DES) guided by angiography alone or guided by FFR measurements. Prior to randomization, lesions requiring PCI were identified based on their angiographic appearance. Patients randomized to angiography-guided PCI underwent stenting of all indicated lesions, while those randomized to FFR-guided PCI underwent stenting of indicated lesions only if FFR was ≤ 0.80 . The primary endpoint was the rate of death, nonfatal myocardial infarction or repeat revascularisation at 1 year.

Results:

Baseline characteristics were similar. The 1-year event rate was 18.3% in the angiography-guided group and 13.2% in the FFR-guided group ($P=0.02$).

Conclusion:

Further follow-up data, subgroup data, and cost-efficiency data will be shown.

Discussant see Presenter report
Thomas Felix Luescher, FESC
(Switzerland)

Survival in patients with heart failure and preserved versus impaired left ventricular ejection fraction: an individual patient data meta-analysis: MAGGIC

Topics: Heart Failure (HF)

Session number: 5027-5028

Session title: Survival in patients with heart failure and preserved versus impaired left ventricular ejection fraction: an individual patient data meta-analysis: MAGGIC



Presenter | see Discussant report
Robert Doughty (New Zealand)

List of Authors:

Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) Investigators

Abstract:

Introduction:

Heart failure with preserved LV ejection fraction (HF-PEF) represents an important subgroup of patients with heart failure. There has been conflicting evidence from previous studies of the outcome for patients with HF-PEF compared with patients with HF with low ejection fraction (HF-lowEF). Hypothesis That patients with HF-PEF have lower mortality than patients with HF-lowEF.

Methods

To investigate survival for patients with HF-PEF we have undertaken an individual patient meta-analysis, combining individual patient data from studies that recruited patients without an LVEF inclusion criterion and reported all-cause mortality. Data, including demographics, medical history, clinical status, LVEF, and all-cause mortality, have been submitted to a central coordinating centre (Auckland, New Zealand) and combined into one dataset. Patients were stratified into 2 groups according to LVEF cut-off: 1) LVEF \geq 50% or HF-PEF; and 2) LVEF <50% or HF-lowEF. Kaplan Meier survival analysis and Cox proportional hazards adjusting for age, gender and study. A separate analysis from the CHARM Cohort was undertaken using similar methods.

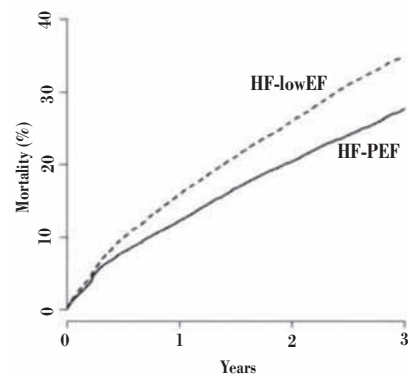
Results

Individual patient data has been submitted from 29 studies, involving 46,596 patients. 25,796 (59%) patients had HF-lowEF, 8571 (20%) HF-PEF and in 9006 (21%) patients LVEF data was missing. For the whole group, mean age 68•12 years, 36% were women, 52% had history of ischemic heart disease and 40% history of hypertension, mean LVEF 37.6 • 15%. The patients with HF-PEF were older (72 • 12 vs 66 • 12), more were women (51% vs 28%), more had a history of hypertension (47% vs 38%) and fewer had ischemic etiology (41% vs 57%) compared with patients with HF-lowEF. During 3 years follow up, 2154 (25%) patients with HF-PEF died compared with 6988 (27%) patients

with HF-lowEF. Using Cox proportional hazards model (adjusting for age and gender and stratifying by study) the HF-PEF group had better survival than the HF-lowEF group (HR 0.68, 95% CI 0.65, 0.72; see figure). A separate analysis of the CHARM cohort using LVEF < or ? 50% demonstrates similar results with the HF-PEF group having better survival than the HF-lowEF group (HR 0.53, 95% CI 0.46, 0.60).

Conclusions

This analysis from a large individual patient data meta-analysis has demonstrated that patients with HF-PEF had better survival than patients with HF-lowEF (similar to that observed within the CHARM cohort). Further clarification of predictors of outcome among patients with HF-PEF may allow future interventions to target high risk subgroups of patients with HF-PEF.



Discussant see Presenter report
David Martin Kaye (Australia)

Report:

The widespread availability of sophisticated diagnostic tools including 2D, Doppler and strain echocardiography and cardiac magnetic resonance imaging together with biomarkers such as brain natriuretic peptide (BNP) has significantly contributed to a major change in the way in which the diagnosis of heart failure (HF) is made. Ostensibly, HF is a clinical diagnosis based upon the recognition of the classic symptoms and signs including dyspnea, edema and fatigue. Following clinical assessment, the rationale for the application of the various investigative techniques in HF patients includes the confirmation of the diagnosis, the development of therapeutic strategies and to provide prognostic information. Coincident with the application of techniques such as echocardiography to large numbers of patients with HF symptoms or in cross-sectional population studies, it has

become evident that approximately half of the HF patients have a normal or near normal left ventricular ejection fraction (HFNEF). In conjunction, these patients exhibit many demographic differences to patients with reduced EF HF (HFREF) including advanced age, history of hypertension, obesity, renal impairment and female gender. Although the distinction between HFNEF and HFREF is now widely accepted, this classification has been the genesis of many more questions. In particular, in contrast to HFREF, the natural history and pathophysiology of HF remains the subject of ongoing debate and in conjunction current therapies for HFNEF are far from satisfactory. The MAGGIC study investigators sought to investigate whether prognosis of HFNEF differs to that for HFREF patients, a point that has recently been debated in the literature. By analyzing a large number of prospective and comparative studies the investigators show in this

study that the prognosis is worse for HFREF patients compared to HFNEF and in this large dataset that LVEF is a key prognostic index, particularly under 30-40%. As observed in other HFNEF studies, affected patients were more likely to be older and to have a history of hypertension. As such, the MAGGIC study serves to remind us that HFNEF patients differ significantly from HFREF patients in many ways, and as a corollary only by clearly understanding its pathophysiology will it be possible to apply or develop specifically targeted therapy.

Notes to editor

The congress reports accompany a presentation given at the ESC Congress 2009 and were written by the author himself/herself and they don't necessarily reflect the opinion of the European Society of Cardiology