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COMMENTS ON CLINICAL TRIALS

The most important clinical trials of the year 2006

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1. INTRODUCTION

The year 2006 was a fruitful year in clinical trials that answered important questions in clinical medicine. The most important questions that have been answered this year were the following 8 ones: 1. what is the efficacy of low molecular weight heparins (LMWH) over the whole spectrum of acute coronary syndromes (ACS); 2. what is the role of first generation drug eluting stents (DES) in primary PCI in acute myocardial infarction comparing with bare metal stents (BMS); 3. how useful is intensive treatment with statins in acute stroke; 4. is the association of clopidogrel to aspirin superior to aspirin alone in primary prevention of stroke; 5. what is the grade of renal failure beyond which angiotensin II converting enzyme inhibitors (ACEI) are no longer useful; 6. what is the optimal modality for prevention in contrast medium induced nephropathy (CIN); 7. what is the prognosis of cardiac arrest in children; and 8. how aggressive should be the insulin treatment in critically ill patients admitted in medical intensive care units (ICU). ❑

2. WHAT WAS KNOWN ABOUT THESE QUESTIONS?

In ACS, antithrombotic treatment is pivotal; unfractioned heparin (UFH) has been the first choice ever since. LMWH have proved to be non-inferior to UFH in unstable angina (UA) and non-ST elevation acute myocardial infarction (NSTEMI). The usefulness of LMWH compared to UFH in ST-elevation acute myocardial infarction (STEMI) was unknown. The efficacy of fondaparinux – a new parenteral anticoagulant that inhibits factor Xa - was not established in patients with ACS, compared with traditional antithrombotic regimen with heparin.

It has been proven that primary PCI is superior to thrombolysis in STEMI. It has also been proven that DESs are superior to BMSs for elective PCI because of significant reduction in in-stent restenosis and target lesion revascularization. Direct comparison of DES versus BMS for primary PCI was made in just one small prospective study (with 148 patients), that showed at 8 months of follow-up a 67% relative risk reduction (RRR) for the combined end-point of death, reinfarction, stroke and restenosis by using DES (1, 2).

Clopidogrel was shown to be superior to aspirin in secondary prevention of stroke in the CAPRIE trial (3) with a RRR of 8.7% for the combined end-point of myocardial infarction, stroke and cardiovascular death. It should be noted that the statistical significance for this result and this combined end-point was marginal (p = 0,047), even if the sample size of this study was huge (about 20.000 patients). The dual antiplatelet therapy has not been investigated in stroke and transient ischemic attacks (TIA), although an indirect conclusion that association of clopidogrel and aspirin might be better than

aspirin alone was extrapolated from clinical trials in ACS.

In a large meta-analysis on over 90,000 patients (4) for primary prevention of stroke, the use of large doses of statins in patients with cardiovascular disease (CVD) was associated to a 21% RRR of stroke. The risk reduction was proportional with LDL reduction: there was a 15% RRR for every 10% reduction in the LDL level. It has been shown that large doses of statins are useful in CVD and statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established. The usefulness of high-doses of statins for secondary prevention in stroke has not been analyzed, and a subgroup analysis of the Heart Protection Study showed no benefit in this respect (5).

According to the loss of glomerular filtration rate (GFR), chronic renal disease (CRD) is divided into 5 stages of severity (6). Stage I is called renal lesion with preserved GFR (GFR > 90 ml/m2/min). Stage II is called mild CRD (GFR 60-89 ml/m2/min). Stage III is called moderate CRD (GFR 30-59 ml/m2/min). Stage IV is called severe CRD (GFR 15-30 ml/m2/min). Stage V is called renal failure (GFR < 15ml/m2/min) and is an indication to renal dialysis if uremia is present. In CRD, ACEI were prescribed only in stage I and II, and they were considered contraindicated in more advanced renal dysfunction.

CIN is a severe complication related with usage of contrast media agents for coronary and interventional procedures, with a high risk of mortality, need for prolonged hospitalization and need for renal-replacement therapy. Patients undergoing urgent procedures (e.g. primary angioplasty) are at higher risk of CIN than are those undergoing elective PCI. Four modalities for preventing the CIN are usually considered (7): non-iodinated contrast agents (associated with a RRR of 50%, but still associated with a significant volume-dependent risk of CIN, induced by quantities of contrast more than 5ml/kg); hidratation (with 1ml/kg/h of normal saline for 24 hours); alcalinization of urine with NaHCO3; and hemofiltration in patients with stage IV or V CRD. The use of N-acetyl cystein (N-ACC) showed a 27% to 46% RRR of CIN in several small studies, yet an unequivocal benefit has not been proved.

The prognosis of cardiac arrest in children has not been systematically studied. Small studies showed that cardiac arrhythmias requiring DC cardioversion occurred between 1 and 29% of the cases. Results from the adult population cannot be applied in children, because of the radical differences between the two populations. The primary disease that leads to cardiac arrest is ischemia and CVD in adults while severe, multiorgan failure represents the main cause in children. The critical mass for maintaining ventricular tachycardia (VT) or ventricular fibrillation (VF) seems to be present less frequent in children due to smaller hearts (hence the rarity of VT and VF in newborns). The proportion of VT/VF versus pulseless electrical activity (PEA) is unknown in children.

Insulin resistance is a very frequent issue in critically ill patients, and is associated with severe prognosis. A usual indication for administering insulin in such patients is hyperglycemia of more than 215 mg/dl. No insulin therapy is considered when blood glucose level is less than 180 mg/dl. The goal of these indications is to maintain a small, but safe level of hyperglycemia and to avoid hypoglycemia. However, obtaining euglycemia (a blood glucose level of 80 to 110 mg/dl) with intensive insulin treatment has been shown to reduce mortality in critically ill surgical patients; intensive insulin treatment reduced the incidence of death to 7% vs. 11% with conservative treatment in non-selected critically ill surgical patients. The benefit of intensive insulin therapy appeared to increase with the severity of patients – a reduction in mortality to 14% from 21% with conservative management in patients that needed ICU treatment for longer than 3 days, and to 17% from 28% in patients that needed ICU treatment for longer than 5 days) (8,9). No data were available for critically ill medical patients. ❑

3. THE ANSWERS

3.1. LMWH versus UFH in STEMI – ExTRACT TIMI 25 trial (10)

The ExTRACT TIMI 25 trial included 20,506 patients with STEMI who were scheduled to undergo fibrinolysis were randomized to receive enoxaparin throughout the index hospitalization or weight-based unfractionated heparin for at least 48 hours. The primary efficacy end point was death or nonfatal recurrent myocardial infarction through 30 days.

There were 3 dose regimens of enoxaparin: in patients younger than 75 years of age enoxaparin (or matching placebo) was to be given as a fixed, 30 mg intravenous bolus followed 15 minutes later by a subcutaneous injection of 1,0 mg/kg every 12 hours. For patients at least 75 years of age, the intravenous bolus was eliminated and the subcutaneous dose was reduced to 0,75 mg/kg every 12 hours. If the creatinine clearance was < 30ml/min the dose was to be modified to 1 mg/day, without bolus. A creatinine level of more than 2,5 mg/dl in men and 2 mg/dl in women was an exclusion criterion. Secondary end-points were defined as a composite of death, reinfarction and emergency revascularization and death, reinfarction and stroke at 30 days, respectively. The results showed that enoxaparine was superior to UFH in both primary and secondary objectives; the benefit of enoxaparin was evident after 48 hours and sustained at 30 days. The primary end point occurred in 12,0% of patients in the unfractionated heparin group and 9,9% of those in the enoxaparin group (17% RRR, p < 0,001). Nonfatal reinfarction occurred in 4.5% of the patients receiving unfractionated heparin and 3.0% of those receiving enoxaparin (33% RRR, p < 0,001); 7,5% of patients given unfractionated heparin died, as did 6,9% of those given enoxaparin (p = 0,11). The composite of death, nonfatal reinfarction, or urgent revascularization occurred in 14,5% of patients given unfractionated heparin and 11,7% of those given enoxaparin (p < 0,001). The benefit was present in all subgroups, with the exception of patients aged over 75 (p = NS) or when streptokinase was used (p = NS). Hemorrhagic complications were higher for STEMI patients treated with enoxaparin compared with UFH, and the differences were significant for both minor and major bleedings. Major bleeding occurred in 1,4% and 2,1%, respectively (p < 0,001). For enoxaparin group, the relative risk for bleeding was on average 1,35, compared with patients treated with UFH. However, the benefit outweighed the risk of bleeding. The composite of death, nonfatal reinfarction, or nonfatal intracranial hemorrhage (a measure of net clinical benefit) occurred in 12,2% of patients given unfractionated heparin and 10,1% of those given enoxaparin (p < 0,001). However, one might criticize the differences seen between UFH and LMWH were due to the study design and not because of a greater efficacy of enoxaparin. Thus, the study cannot discriminate whether the results are due to a higher efficacy of LMWH over UFH, or to a longer duration of treatment with LMWH (7 days versus 2 days with UFH), or to a thrombotic rebound after stopping UFH after day 2 (the curves divided after day 2; in the first two days the curves for UFH and LMWH almost completed overlapped). ❑

3.2. Fondaparinux versus LMWH in UA/ NSTEMI and STEMI – OASIS 5 trial (11) and OASIS 6 trial (12)

OASIS 5 clinical trial included 20,078 patients with UA and NSTEMI that were randomized towards receiving fondaparinux 2,5 mg or enoxaparin 1mg/kg twice daily, for a mean duration of 6 days. Primary objective was a composite of death, reinfarction and refractory ischemia at 9 days. Patients were followed up for 6 months. There were no differences in primary objective at 9 days, but the hemorrhagic risk was significantly less with fondaparinux as compared to enoxaparin (217 events [2,2%] vs. 412 events [4,1%]; hazard ratio, 0,52; p < 0.001). At 180 days there was a significant 19% RRR in the risk of death associated with fondaparinux compared with enoxaparin (p = 0,05), and a similar reduction in relative risk for the composite end-point of death, reinfarction and stroke (p = 0,007). This benefit associated with fondaparinux at 180 days was entirely due to the reduction of hemorrhagic complications compared with enoxaparin.

OASIS 6 was conducted to evaluate the effect of fondaparinux, a factor Xa inhibitor, when initiated early and given for up to 8 days versus usual care (placebo in those in whom UFH is not indicated [stratum 1] or UFH for up to 48 hours followed by placebo for up to 8 days [stratum 2]) in patients with STEMI. The trial included 12,092 patients with STEMI. Primary objectives were the rate of death and reinfarction at 30 days, with secondary assessments at 9 days and at final follow-up (3 to 6 months). Overall, fondaparinux was found to be better than placebo at 30 days, but there were no differences found compared to UFH. However, there was no benefit in those undergoing primary PCI. In other patients in stratum 2, fondaparinux was superior to UFH in preventing death or reinfarction at 30 days (HR, 0,82; 95% CI, 0,66-1,02; p = 0,08) and at study

end (HR, 0,77; 95% CI, 0,64-0,93; p = 0,008). Significant benefits were observed in those receiving thrombolytic therapy (HR, 0,79; p = 0,003) and those not receiving any reperfusion therapy (HR, 0,80; P = 0,03). There was a tendency to fewer severe bleeds (79 for placebo vs 61 for fondaparinux; p = 0,13), with significantly fewer cardiac tamponade (48 vs 28; p = 0,02) with fondaparinux at 9 days. In conclusion, OASIS 6 trial showed that in patients with STEMI, particularly those not undergoing primary PCI, 2,5 mg of fondaparinux daily significantly reduces mortality and reinfarction without increasing bleeding and strokes, without the need for anticoagulant monitoring.

From ExTRACT TIMI 25 and OASIS 5 and 6 trials we can conclude that LMWH are the treatment of choice in all clinical conditions of ACS instead of UFH. In patients receiving fibrinolysis for STEMI, treatment with enoxaparin throughout the index hospitalization is superior to treatment with UFH for 48 hours but is associated with an increase in major bleeding episodes. Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at 9 days in patients with UA or NSTEMI, but it substantially reduces major bleeding and improves long term mortality and morbidity. In patients with STEMI, particularly those not undergoing primary PCI, fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes. ❑

3.3. DES or BMS for primary PCI in STEMI – PASSION and TYPHOON trials (13,14)

PASSION and TYPHOON trials have similar design. They both included patients with STEMI who were followed for 12 months. The primary endpoint in both trials was a composite of death from cardiac causes, reinfarction and target-lesion revascularization at 1 year. PASSION trial included 619 patients from 2 centers and randomized them towards paclitaxel eluting stent Taxus or BMS with the same metallic platform as Taxus stent (Express 2). TYPHOON trial included 712 patients from 48 centers and randomized them towards sirolimus eluting stent Cypher or any BMS. In PASSION there was a trend toward a lower rate of serious adverse events in the paclitaxel-stent group than in the uncoated-stent group (8,8% vs. 12,8%; adjusted relative risk, 0,63; 95% confidence interval, 0,37 to 1,07; p = 0,09). A nonsignificant trend was also detected in favor of the paclitaxel-stent group, as compared with the uncoated-stent group, in the rate of death from cardiac causes or recurrent myocardial infarction (5,5% vs. 7,2%, p = 0,40) and in the rate of target-lesion revascularization (5,3% vs. 7,8%, p = 0,23). The incidence of stent thrombosis during 1 year of follow-up was the same in both groups (1,0%). Although the use of paclitaxel-eluting stents in acute myocardial infarction with ST-segment elevation reduced the incidence of serious adverse cardiac events at 1 year by 4%, as compared with BMS, the difference was not statistically significant. In TYPHOON, the rate of the primary end point was significantly lower in the sirolimus-stent group than in the BMS group (7,3% vs. 14,3%, p = 0,004). This reduction was driven by a decrease in the rate of target-vessel revascularization (5,6% and 13,4%, respectively; p < 0,001). There was no significant difference between the 2 groups in the rate of death (2,3% and 2,2%, respectively; p = 1,00), reinfarction (1,1% and 1,4%, respectively; p = 1,00), or stent thrombosis (3,4% and 3,6%, respectively; p = 1,00). The investigators concluded that among selected patients with acute myocardial infarction, the use of sirolimus-eluting stents significantly reduced the rate of target-vessel revascularization at 1 year. The differences between two trials in terms of efficacy of sirolimus- and paclitaxel-eluting stents in patients with STEMI undergoing primary PCI might be explained by the differences in the BMSs that were used; in TYPHOON, it was permitted the use of any BMS, with different metallic support structures, as compared with PASSION where the metallic support was similar in DES and BMS. ❑

3.4. Primary and secondary prevention in stroke

CHARISMA trial (15) included 15,603 patients with ischemic heart disease or multiple risk factors for CVD. The trial assessed the efficacy of clopidogrel plus aspirin versus aspirin alone in the primary prevention of stroke. The primary objective at 28 months (a composite endpoint of myocardial infarction, stroke and cardiovascular death) did not differ between the 2 groups, and there were no differences in any of the subgroups analyzed (patients with multiple risk factors for CVD or patients with clinically evident atherothrombosis).

SPARCL trial (16) included 4,371 patients with history of stroke or TIA within 1 to 6 months before study entry, who had a LDL level between 100 and 190 mg/dl and no evident coronary heart disease. Patients were randomized to receive atorvastatin 80mg or placebo. The primary objective at a median follow-up of 4,9 years was the total incidence of stroke (first fatal and non-fatal stroke). The study showed that atorvastatin 80mg was more efficient than placebo in secondary prevention of stroke 11,2% incidence of fatal and non-fatal stroke in atorvastatin group vs. 13,1% in placebo group, with a 5-year absolute reduction in risk (ARR) of 2,2% (adjusted hazard ratio, 0,84; 95 percent confidence interval, 0,71 to 0,99; p = 0,03; unadjusted p = 0,05). As expected, the beneficial effect of statin therapy on the risk of recurrent stroke was due to a reduction in the risk of cerebral infarction, the mechanism of which largely has been attributed to a reduction in LDL cholesterol levels. The lower average LDL cholesterol level achieved in the atorvastatin as compared with the placebo group is consistent with this hypothesis. Other putative mechanisms include a variety of possible pleiotropic effects.

Although at enrollment patients had no known coronary heart disease, the risk of cardiovascular events, including major coronary events and revascularization procedures, was also substantially reduced. The 5 year ARR of major cardiovascular events was 3,5% (hazard ratio, 0,80; 95 percent confidence interval, 0,69 to 0,92; p = 0,002). These benefits were observed despite the increased use of open-label nonstudy statins during the study, a result suggesting that the effect is robust.

The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group (p = 0,98), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin (2,2% versus 0,5%).

These results are in contrast with Heart Protection Study, where there was no difference between statin and placebo in secondary prevention of stroke (10,4% of patients in the statin group had a recurrent stroke, as compared with 10,5% of patients in the placebo group). A possible explanation for this difference in results is that patients in the HPS were enrolled an average of 4,3 years after the index event, whereas the risk of recurrence is highest within the first years after stroke. Another explanation may be the larger reduction in LDL cholesterol in SPARCL study than in the HPS (56 mg/dl vs. 39 mg/dl). ❑

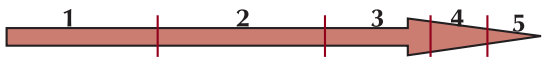
3.5. ACEI in advanced stages of Chronic Renal Disease (17)

The first large clinical trial that assessed the safety and utility of ACEI in advanced stages of CRD (stage III and IV) was published in the beginning of 2006 in the New England Journal of Medicine. The results were impressive. This study included 422 non-diabetic patients that were divided in 2 groups according to the creatinine level. Group 1 had a serum creatinine level between 1,5 and 3 mg/dl. This group received benazepril 20mg twice daily. The second group had a creatinine level between 3 and 5 mg/dl. This group was randomized to receive benazepril 20 mg twice daily or placebo. Patients were followed-up for a median of 3,4 years. Primary objective was a combined end-point between the rate of doubling of serum creatinine, evolution towards end-stage renal disease (ESRD, CRD stage V) and death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease. The results showed that in stage III and IV CRD (creatinine level of 3 to 5 mg/dl, group 2) benazepril 20mg daily lead to a 20% ARR of the primary end-point as compared with placebo; benazepril was associated with a 43% reduction in the risk of the primary end point in group 2 (p = 0,005). This benefit did not appear to be attributable to blood-pressure control. Benazepril therapy was associated with a 52% reduction in the level of proteinuria and a reduction of 23% in the rate of decline in renal function. This translates into a doubling of the time of progression towards ESRD, from 3,5 years to 7 years. The overall incidence of major adverse events in the benazepril and placebo subgroups of group 2 was similar. This study showed that benazepril conferred substantial renal benefits in patients without diabetes who had advanced renal insufficiency, if careful monitoring of potassium and creatinine levels are provided (Figure 1). This conclusions may come as news to the many clinicians who avoid or abandon the use of ACE inhibitors or angiotensin-receptor blockers in their patients with stage III and IV chronic renal disease, fearing that

this approach merely increases risk (especially of hyperkalemia) without providing benefit (e.g., slowing the decline in GFR). However, the results of this study should be taken with some caution (18). The study included only Chinese patients. There was no significant increase in potassium level in patients that were treated with ACEI. This might be a consequence of the fact that 80% of the patients received a diuretic during follow-up, there is a low level of protein intake in Chinese population (about half comparing with Western patients) and that 5% of the patients were excluded during enrolment because of hyperkalemia. The study does not also clarify when be treatment with an ACE inhibitor should stopped in patients with advanced stages of CRD. Abandoning treatment with ACE inhibitors or angiotensin-receptor blockers in patients with advanced stages of CRD seems to be unnecessary, in absence of uncontrolled hyperkalemia. ❑

3.6. N-ACC for the prevention of contrast medium induced nephropathy (19)

Patients with acute myocardial infarction undergoing primary angioplasty are at high risk for CIN because of hemodynamic instability, the need for a high volume of contrast medium, and the lack of effective prophylaxis. 354 patients with STEMI assigned to primary PCI were included in a study that analyzed the efficiency of N-ACC in the prevention of CIN. Patients were randomized into 3 groups to receive placebo, N-ACC in standard dose (600 mg IV bolus before PCI followed by 600 mg orally twice daily for 48 hours after intervention), and N-ACC high dose (1200 mg IV bolus and 1200 mg orally twice daily for 48 hours after angioplasty). Primary objective was the incidence of CIN defined as a 25% increase of the creatinine level from baseline in the first 72 hours after PCI. Secondary objectives were in-hospital MACE and in-hospital mortality. The incidence of CIN was 33% in control patients, 15% in patients receiving standard dose of N-ACC, and 8% in patients receiving high-dose N-ACC ($p < 0,001$). This beneficial effect of high-dose N-ACC in preventing CIN was not related to baseline creatinine clearance (baseline renal function) and left ventricular ejection fraction (LVEF). Remarkably, N-ACC looked like to prevent CIN in patients with normal renal function and in those with baseline reduce renal function, as well as in patients with mild or severe impairment of left ventricular systolic function. Overall in-hospital mortality was higher in patients with CIN than in those without such nephropathy (26% vs. 1%, $p < 0,001$). Thirteen patients (11%) in the control group died, as did 5 (4%) in the standard-dose N-ACC group and 3 (3%) in the high-dose N-ACC group ($p = 0,02$). The rate for the composite end point of death, acute renal failure requiring temporary renal replacement therapy, or the need for mechanical ventilation was 21 (18%), 8 (7%), and 6 (5%) in the 3 groups, respectively ($p = 0,002$). N-ACC prevented the occurrence of CIN in a dose-dependent fashion, with maximal benefit for the highest dose (double standard dose), regardless of the presence of baseline renal or left ventricular dysfunction. In-hospital mortality was higher in patients who developed CIN. ❑



	Stage I	Stage II	Stage III	Stage IV	Stage V
stage	Renal lesion with preserved GFR	Mild Chronic Renal Disease (CRD)	Moderate CRD	Severe CRD	Renal failure
GFR (ml/min/1,73m2)	> 90	60-89	30-59	15-30	<15
ACEI?	Yes	Yes	Yes	Yes	?

FIGURE 1. Current indications for the use of angiotensin II converting enzyme inhibitors (ACEI) in chronic renal disease
Note: GFR, glomerular filtration rate

3.7. The prognosis of cardiac arrest in children (20)

The National Registry of CPR examined 1005 cases of in-hospital pediatric cardiac arrest from 159 medical centers in the United States. Any etiology of the cardiac arrest (any primary disease) was included. The results are shown in Figure 2. The study showed that there are major differences in the prognosis and in the type of cardiac arrest in children compared with adults. Arrhythmias, the treatment of which requires DC shock (VT/VF) are less frequent than in the adult population, but their incidence is higher than expected from previous data. Surprisingly,

the worst prognosis is not associated with non-shockable rhythms (like PEA) but with VT/VF that occurs during resuscitating maneuvers. The best prognosis is associated with primary VT/VF; however, in-hospital survival rate is lower in children than in the adult population (34%). ❑

3.8. Intensive insulin treatment in medical critically ill patients (21)

This study included 1,200 patients admitted to an ICU due to any severe medical illness. Patients were randomized to receive insulin infusion as to obtain strict normalization of blood glucose levels (80-110 mg/dl) or to conventional insulin treatment (insulin administered when blood glucose level exceeded 215 mg/dl, and insulin doses reduced when the level fell below 180 mg/dl). The primary objective was in-hospital mortality. Secondary objectives were mortality in the ICU and at 90 days, the need for mechanical ventilation, the need for dialysis, and the incidence of acute renal failure. Intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40,0% in the conventional-treatment group vs. 37,3% in the intensive-treatment group, p = 0,33). Intensive insulin therapy was associated with lower in-hospital morbidity as compared with standard care, by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. Mortality was reduced by about 10% (ARR) at 90 days in patients who stayed in ICU for longer than 3 days (p = 0,02). However, this subgroup that benefited in terms of mortality could not be identified prior to inclusion. Therefore, the authors concluded that intensive insulin therapy, targeting normalization of blood glucose level might be recommended in all critically ill patients admitted in ICU. ❑

4. CONCLUSION

The answer to the 8 questions stated in the Introduction can be summarized as follows:

1. LMWH (enoxaparin) is probably superior to UFH in the whole spectrum of ACS including STEMI; fondaparinux is similar to enoxaparin in reducing recurrent ischemic events in non-ST segment elevation ACS, and improves long term outcome by reducing the risk of bleeding; fondaparinux may represent an alternative to heparin in patients with STEMI not undergoing primary angioplasty and at high hemorrhagic risk.

2. DES seems to be superior to BMS for primary PCI in STEMI; however, the cost-effectiveness and long-term safety of DES compared with BMS needs further assessment;

3. Adding clopidogrel to aspirin in primary prevention of stroke in high risk patients is ineffective;

4. The use of statins for secondary prevention of stroke is useful, providing high doses are used, that will lower LDL-cholesterol level by 50% to 60% from baseline;

5. ACE inhibitors, particularly benazepril are indicated from mild to severe CRD as long as careful monitoring of creatinine and potassium level is made; ACEI may have the ability to double the time of evolution towards ESRD of stage III and IV CRD;

6. N-ACC is efficient in preventing CIN in a dose-dependent manner, even in patients

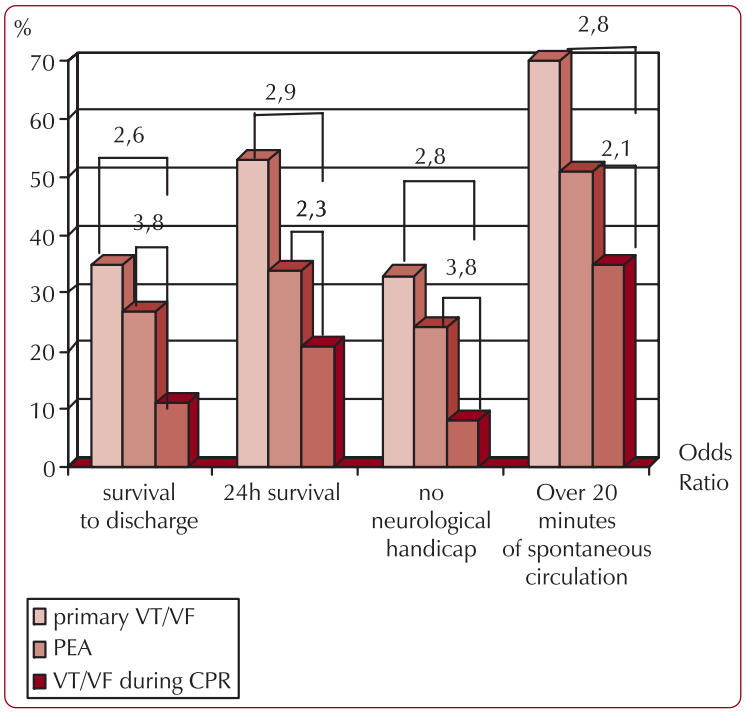


FIGURE 2. The prognosis of cardiac arrest in children
Numbers denote the relative risk of death between different types of cardiac arrest.
Note: VT, ventricular tachycardia; VF, ventricular fibrillation; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation.
Data from reference 20.

with normal renal function undergoing primary PCI;

7. The pattern and prognosis of cardiac arrest in children is different from the adult population; shockable rhythms are frequent even in children with cardiac arrest. The worst prognosis is associated with VT/VF that develop during resuscitation maneuvers;
8. Critically ill patients admitted in ICU, either diabetic or not, should receive intensive insulin therapy to normalize blood glucose level, if they present hyperglycemia at admission. This approach significantly reduces the morbidity, and a benefit on mortality is evident in patients needing more than three days staying in ICU. ❑

REFERENCES

1. **Valgimigli M, Percoco G, Malagutti P, Campo G, Ferrari F, Barbieri D, Cicchitelli G, McFadden EP, Merlini F, Ansani L, Guardigli G, Bettini A, Parrinello G, Boersma E, Ferrari R, for the STRATEGY Investigators** – Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent for Acute Myocardial Infarction. *JAMA* 2005; 293:2109-2117
2. **Van de Werf F** – Drug-eluting stents in acute myocardial infarction. *N Engl J Med* 2006; 355:1169-1170
3. **CAPRIE Steering Committee** – A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996; 348:1329-39
4. **Amarenco P, Labreuche J, Lavallée P, Touboul PJ** – Statins in Stroke Prevention and Carotid Atherosclerosis. *Stroke* 2004; 35:2902-1909
5. **Heart Protection Study Collaborative Group** – Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004; 363:757-767
6. **Levey AS** – Nondiabetic kidney disease. *N Engl J Med* 2002; 347:1505-1511
7. **Barrett BJ, Parfrey PS** – Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006; 354:379-86
8. **Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R** – Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359-1367
9. **Van Den Berghe G, Wouters PJ, Bouillon R, et al.** – Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med* 2003; 31:359-66
10. **Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, López-Sendón JL, Guneri S, Jiang F, White HD, Fox KAA, Braunwald E, for the ExTRACT-TIMI 25 Investigators** – Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006; 354 published online on March 14, 2006 at www.nejm.org
11. **The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators** – Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; 354 published online on March 14, 2006 at www.nejm.org
12. **The OASIS-6 Trial Group** – Effects of fondaparinux on mortality and reinfarction in patients with acute ST-elevation myocardial infaction. The OASIS-6 Randomized Trial. *JAMA* 2006; 295:(doi:10.1001/jama.295.13.joc60038) published online on March 14, 2006 at www.jama.com
13. **Laarman GJ, Suttorp MJ, Dirksen MT, van Heerebeek L, Kiemeneij F, Slagboom T, van der Wieken LR, Tijssen JGP, Rensing BJ, Patterson M** – Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006; 355:1105-1113
14. **Spaulding C, Henry P, Teiger E, Beatt K, Bramucci E, Carrie D, Slama MS, Merkely B, Erglis A, Margheri M, varenne O, Cebrian A, Stoll HP, Snead DB, Bode C, for the TYPHOON Investigators** – Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006; 355:1093-1104
15. **Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J and Topol EJ, for the CHARISMA Investigators** – Clopidogrel and aspirin versus aspirin alone for the prevention of atheroembolic events. *N Engl J Med* 2006; 354:1706-1717
16. **The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators** – High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355:549-559
17. **Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW** – Efficacy and safety of benazepril for advanced chronic renal isufficiency. *N Engl J Med* 2006; 354:131-140
18. **Hebert LA** – Optimizing ACE-inhibitor therapy for chronic renal disease. *N Engl J Med* 2006; 354:189-191
19. **Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL**

– N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006; 354:2773-2782

20. **Samson RA, Nadkarni VM, Meaney PA, Carey SM, Berg MD, Berg RA, for the American Heart Association National Registry of CPR Investigators** – Outcome of in-hospital ventricular fibrillation in children. *N Engl J Med* 2006; 354:2328-2339
21. **Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R** – Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449-461

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