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Scientific Update™

Clinical Trial Hotlines: Preliminary Results from the XXth Congress of the European Society of Cardiology

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Heart failure studies (CIBIS-II and MACH-I)
reported by GORDON MOE, MD

CAD trials (BIP, GUSTO-III, TIMI IIB, and FRAX.I.S)
reported by SHAUN GOODMAN, MD

The XXth Congress of the European Society of Cardiology met in Vienna this past summer. This update gives a brief but clinically relevant overview of the information presented about several heart failure and CAD studies. The CIBIS-II trial demonstrates for the first time that bisoprolol improves all-cause mortality in patients with heart failure. MACH-1 results strongly argue for continuing careful post-market surveillance of newly-approved drugs beyond the experience of phase-III protocols. The BIP trial showed once-daily bezafibrate treatment for patients with established CAD to be ineffectual in improving outcome. After one year, GUSTO-III results are showing no difference between r-PA and t-PA. Results from TIMI-IIB show the superiority of enoxaparin over unfractionated heparin for patients with non-persistent ST-segment elevation ischemic syndromes. In contrast, FRAX.I.S. data do not show the same advantage from nadroparin use. The OASIS-II trial does show that hirudin is superior to unfractionated heparin in patients with unstable angina and non-Q-wave MI.

CIBIS-II

ß-adrenergic receptor blockade has rapidly evolved as one of the most promising approaches to reduce mortality and morbidity in patients with heart failure. Until recently, the only ß-blocker studies demonstrating a reduction of all-cause mortality have involved carvedilol,[1,2] a non-selective ß-blocker with ancillary properties such as α-adrenergic blockade and antioxidant properties.[3]

In the Cardiac Insufficiency Bisoprolol Study I (CIBIS-I), 641 patients with heart failure of mixed etiologies with New York Heart Association (NYHA) class III (95%) and IV (5%) symptoms and left ventricular ejection fraction (LVEF) <40% were randomized to receive the selective ß-1 adrenergic receptor blocker bisoprolol or placebo.[4] Results of CIBIS-I indicated that patients treated with bisoprolol had a significant reduction in hospitalization for heart failure. However, the 20% reduction of total mortality at 2 years did not reach statistical significance.

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Table 1: CIBIS-II selected demographic data

	Placebo	Bisoprolol
Ischemic etiology	58.1%	59.8%
Male	80.5%	80.6%
NYHA class III symptoms	83.3%	83.0%
NYHA class IV symptoms	16.7%	16.3%

CIBIS-II evaluated the effect of bisoprolol on mortality in patients with ischemic or non-ischemic chronic heart failure. Details of its rationale and design have been reported previously.[5] In brief, 2647 patients with chronic heart failure and NYHA III and IV symptoms with LVEF<35% were randomized to placebo or bisoprolol. Medication was initiated at 1.25 mg orally daily and titrated up to 10 mg daily. The primary endpoint was all-cause mortality and the secondary endpoints included hospitalizations, cardiovascular mortality, and permanent treatment withdrawal.

The first patient was randomized to treatment in November 1995. The planned follow-up was a minimum of 3 years. Selected demographics data are summarized in Table 1. The trial was stopped prematurely after the second interim analysis conducted in March 1998 because of a survival benefit attributable to bisoprolol. As a result, the mean follow-up was 1.4 years. The all-cause mortality was significantly reduced (Figure 1). In the subgroup analysis of pre-specified variables, the favorable effect of bisoprolol on mortality was similar regardless of age, ischemic versus non-ischemic etiology, and NYHA class. As can be seen in Table 2,

Figure 1: Mortality benefit

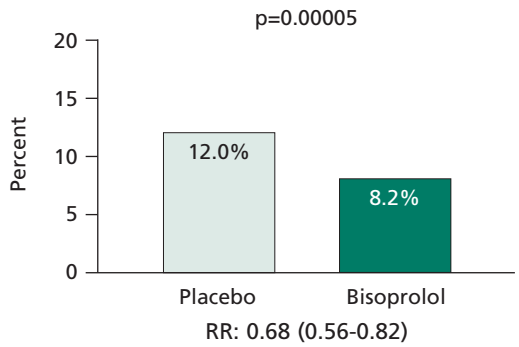


Table 2: CIBIS-II mortality data according to cause

Cause	Placebo	Bisoprolol	Probability
Sudden death	6.4%	3.6%	0.001
Pump failure	0.6%	0.5%	0.250
MI	0.6%	0.5%	0.780
Non-cardiovascular	1.4%	1.1%	0.470
Unknown	3.7%	1.7%	0.002

besides producing a 32% reduction in all-cause mortality, bisoprolol also reduced sudden death by 45% with no adverse impact on mortality due to other causes. Data on hospital admissions are shown in Table 3. Bisoprolol reduced hospitalizations due to all causes, including a 30% reduction of hospital admissions due to worsening heart failure.

Results of CIBIS-II lend further support to the concept that ß-blockers reduce mortality and morbidity in patients with heart failure. However, since the overall mortality rate of the patients in CIBIS-II was relatively low compared with previous heart failure trials on patients with NYHA classes III and IV symptoms, it is unclear whether the data of CIBIS-II are applicable to all patients with heart failure, especially those with truly advanced disease. In addition, the relative benefit of selective ß-1 receptor blockade versus non-specific ß-receptor blockade with or without ancillary vasodilator and antioxidant properties remains to be examined. The answers to these questions will await the completion of ongoing trials such as MERIT-HF, BEST, COMET, and COPERNICUS.

MACH-1

T-channel calcium blockade is a potentially promising novel treatment for various cardiovascular disorders.[6] Mibefradil (Ro 40-5967) was the only T-channel calcium blocker available for clinical use. However, on June 8, 1998,

Table 3: CIBIS-II hospital admission data

Cause	Placebo	Bisoprolol	Probability
All-cause	39.6%	33.6%	0.002
Heart failure	17.6%	11.9%	0.00005
V-tachycardia	1.5%	0.5%	0.006
Non-cardiovascular	14.1%	11.5%	0.05

the agent was voluntarily withdrawn from the market by the sponsor because of its interaction with other medications. This report will briefly review the results of the only heart failure trial conducted on mibefradil.

The Mortality Assessment in Congestive Heart Failure (MACH-1) study was an international double-blind placebo-controlled trial designed to assess the effect of mibefradil on survival in patients with heart failure (NYHA classes II to IV symptoms) and on optimal medical therapy. The primary endpoint was all-cause mortality. To be eligible for the study, a patient must have had a LVEF <35% and be unable to walk more than 400 m in the 6-minute walk test. The details of the design of MACH-1 have been recently reported.[7] The first patient entered the study in October 1994, and the last patient was randomized to treatment on 25 October 1996.

A total of 2,590 patients (1,295 patients for both placebo and mibefradil) was enrolled. The average followup was 24 months. The mean LVEF was 24.6% and 24.4% for the placebo and mibefradil groups, respectively. There was no statistically significant difference between placebo and mibefradil on the primary endpoint of total mortality (12% excess in mibefradil, not significant) as well as the secondary endpoints of cardiovascular mortality, cardiovascular morbidity (defined as dropout for heart failure, hospitalizations for worsening heart failure or angina, myocardial infarction, stroke or other cardiovascular events), or combined cardiovascular mortality and morbidity. However, women and patients with atrial fibrillation had significant higher mortality with mibefradil. Furthermore, patients who were treated with any agents known to be associated with torsades de pointe (amiodarone, erythromycin, amytriptyline, cisapride, sotalol, procainamide and quinidine, terfenadine) all had significantly higher mortality when treated with mibefradil, presumably because of drug interaction.

Results of the MACH-1 study highlight some of the difficulties of drug development in a contemporary environment where patients with cardiovascular disorders not infrequently receive multiple concurrent medications. Mibefradil is known to inhibit cytochrome P450 2D6 and 3A4, and therefore, could increase the plasma concentrations of concomitantly prescribed drugs to potentially dangerous levels. Accordingly, while mibefradil itself may not be harmful to patients, its ability to increase the concentrations of other concurrent medications may be harmful. The experience with mibefradil and the results of the MACH-1 study strongly argue for continuing careful postmarket surveillance of newly-approved drugs beyond phase-III protocols.

BIP

The Bezafibrate Infarction Prevention (BIP) trial evaluated the once-daily use of bezafibrate (400 mg) in patients with established coronary artery disease.[8] BIP was randomized, double-blind, placebo-controlled and enrolled 3,090 patients (91% male, mean age 60 years) who were eligible for study inclusion if they had sustained a myocardial infarction (MI) (within 6 months to 5 years) or had had angina for at least 2 years. In addition, their baseline profiles included a total cholesterol of 3.89–6.48 (mean 5.49) mmol/L, low-density lipoprotein (LDL) ≤4.66 (mean 3.83) mmol/L, high-density lipoprotein (HDL) ≤1.17 (mean 0.91) mmol/L, and triglycerides ≤3.39 (mean 1.64) mmol/L.

At a mean of 6.2 (minimum 5) years followup, there were no differences in the composite endpoints of fatal or non-fatal MI, or sudden death (p=0.27). A 9% lower rate of all-cause mortality among bezafibrate-treated patients was also insignificant. In a secondary analysis of those patients whose baseline triglycerides were >2.26 mmol/L, there was a 40% relative reduction in the composite endpoint of death or myocardial infarction (p=0.03).

These results are disappointing, particularly in view of a previous small (n=92) randomized, placebo-controlled trial (Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT]) that showed that bezafibrate (200 mg 3 times

daily) slowed progression of coronary artery stenoses in young MI survivors and reduced coronary events (3 versus 11 patients, p=0.02).[9] Despite significant lowering of serum concentrations of cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglycerides, and a modest increase in HDL levels, LDL concentrations did not change substantially with bezafibrate. In addition, bezafibrate (and other fibrates) have well-defined effects on hemostatic functions that include reducing the concentration of plasma fibrinogen. While lowered fibrinogen levels might have influenced disease progression in the BECAIT, this and other bezafibrate effects failed to translate into significant clinical benefit in the larger BIP study.

GUSTO-III: One-year results

The initial (30 day) results of the GUSTO-III trial have already been published;[10] one-year followup has now been completed in 97% of patients. GUSTO-III enrolled 15,059 patients of any age with acute MI, ST segment elevation, and symptom duration less than 6 hours. All-cause mortality at 30 days (the primary trial end-point) was similar among patients treated with r-PA and accelerated t-PA (7.49% versus 7.26%; absolute difference -0.23%; 95% confidence intervals [CI], 1.12%, 0.66%; p=0.6). At one years' time, the mortality rates remained similar among the two treatment groups (11.21% versus 11.00%; absolute difference -0.21%; 95% CI, 1.29, 0.87; p=0.66).

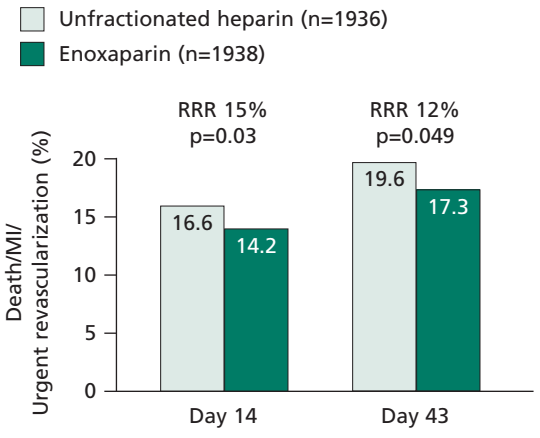
The one-year data are consistent with those seen at 30 days and suggest no advantage of r-PA over accelerated t-PA. Since the 95% confidence intervals around the one-year point estimate continue to overlap, one cannot exclude the possibility that r-PA treatment leads to 1% higher mortality rates than accelerated t-PA (in other words, similar to the 1% worse outcome with streptokinase as compared to t-PA seen in the larger GUSTO-I trial).

TIMI-11B

The Thrombolysis In Myocardial Infarction (TIMI) 11B study compared the efficacy and safety of unfractionated heparin with the low molecular weight (LMW) heparin enoxaparin in patients with non-persistent ST-segment-elevation ischemic syndromes. Patients (n=3,910) with unstable angina or non-Q-wave MI were randomized within 24 hours of chest pain onset to intravenous heparin (70 U/kg bolus followed by 15 U/kg continuous infusion to maintain a partial thromboplastin time [PTT] between 1.5–2.5) for at least 72 hours, or to enoxaparin (initial IV 30-mg bolus followed by 1 mg/kg twice daily subcutaneous injections). After IV therapy was stopped, twice daily subcutaneous injections (placebo versus enoxaparin) were continued in a double-blind fashion up to 43 days.

As seen in figure 2, the primary efficacy endpoints of death, MI, or severe recurrent ischemia requiring revascularization were significantly lower among patients treated with enoxaparin rather than unfractionated heparin (14.2% versus 16.6%, relative risk reduction [RRR] 15%, p=0.03). The rates of major hemorrhage during the initial 72 hours (0.8% versus

Figure 2: Composite endpoints in TIMI-IIB at days 14 and 43



0.7%) and hospital phase (1.5% versus 1%) were similar among the enoxaparin- and unfractionated heparin-treated groups.

By day 43, the composite endpoint remained lower in enoxaparin-treated patients (17.3% versus 19.6%, RRR 12%, p=0.049). Thus, there was no further relative decrease in events with enoxaparin over placebo after the acute phase.

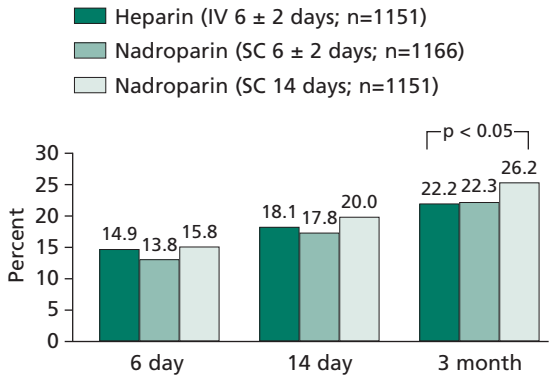
A preliminary meta-analysis combining the ESSENCE[11,12] and TIMI-11B study results at days 8, 14, and 43 reveals a consistent approximate 20% relative risk reduction in the occurrence of death, MI, or urgent revascularization and in death or MI alone.

FRAX.I.S

The FRAX.I.S study compared the efficacy of unfractionated heparin (administered for 6±2 days) to the LMW heparin nadroparin (IV bolus then twice-daily subcutaneous injections for 6±2 or 14 days). As figure 3 shows, there were no differences between the treatment groups with respect to the composite endpoint (death, MI, refractory or recurrent angina) at 6 days (14.9% versus 13.8% versus 15.8%) or 14 days (18.1% versus 17.8% versus 20%). However, at 3 months, there was a higher event rate in patients who received 14 days of nadroparin therapy (26.2%) versus unfractionated heparin (22.2%) (p<0.05).

Thus, in contrast to the consistent results with enoxaparin in the ESSENCE and TIMI-11B studies, there was no apparent advantage of nadroparin over unfractionated heparin in 3,460 patients with unstable angina or non-Q-wave MI. While nadroparin has a similar anti-Xa:IIa ratio as enoxaparin (approximately 3:1 versus unfractionated heparin's 1:1), the apparently different large-scale clinical results with different LMW heparins suggest that further study is required before one can be confident that this is a "class effect" in acute coronary syndromes.

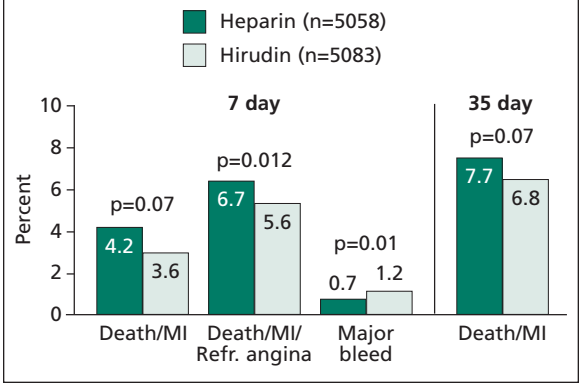
Figure 3: Composite endpoints (death/MI/ refractory angina) in FRAX.I.S. at days 6, 14 and month 3



OASIS-II

This randomized, double-blind trial of 10,141 patients compared intravenous unfractionated heparin (5,000 U bolus followed by 15 U/kg/hr infusion) and intravenous hirudin, a direct thrombin inhibitor, (0.4 mg/kg bolus followed by 0.15 mg/kg/hr infusion) in patients with unstable angina and non-Q-wave MI. In addition, patients received ASA or ticlopidine on a daily basis. As seen in figure 4, the primary composite endpoint of 7-day death and MI was lower among the hirudin-treated patients (3.6% versus 4.2%; odds ratio 0.83, 95% CI, 0.69, 1.01; p=0.07). The secondary

Figure 4: Preliminary results in OASIS-2 at days 7, 35



endpoint of death, MI, and refractory angina was significantly lower among hirudin-treated patients (5.6% versus 6.7%, p=0.012). Although the rates of stroke (0.3% in each group) were similar in the two treatment groups, there was a slight and statistically significant increase in major hemorrhage in the hirudin group (1.2% versus 0.7%, p=0.01). At 35 days, the combined death and MI rate remained lower among hirudin-treated as compared to heparin-treated patients (6.8% versus 7.7%, p=0.07).

When combining the OASIS-I (pilot)[13] and OASIS-II study results, there was evident a significant reduction in the composite endpoint of death and MI at 7 days (hirudin 3.5% versus heparin 4.3%, p=0.034). In a preliminary meta-analysis including both OASIS trials and the GUSTO-IIb[14] (ST and non-ST segment elevation) and TIMI 9B[15] (ST elevation) trials, there was a consistent benefit of hirudin over unfractionated heparin at 72 hours (3.2% versus 4.2%, p=0.0004), 7 days (4.9% versus 5.8%, p=0.013), and 30–35 days (8.1% versus 9.0%, p=0.013).

Summary

The results of these trials should translate into better care for cardiovascular patients. The presented evidence suggests that better outcomes can be achieved in selected patients with heart failure when they are treated with ß-blockers. There is accumulating evidence of benefit from more focused antithrombotic treatment of patients with acute ischemic syndromes.

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