SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

Update on Clinical Trials

Selected Clinical trials at the 48th Annual Scientific Session of the American College of Cardiology

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This *Cardiology Scientific Update* is intended to provide you with a brief and rapid overview of selected clinical trials that were presented at the American College of Cardiology meeting. The format of the presentation focuses on final results rather than an in-depth review of the methodology or the clinical implications.

MERIT-HF Study: Metoprolol in CHF

The purpose of this study was to investigate the efficacy of metoprolol, in addition to standard therapy, in reducing mortality in patients with NYHA class II-IV congestive heart failure (CHF) (Table 1).

Importantly, there was a 38% relative risk reduction in cardiovascular death, 41% relative risk reduction in sudden death, and 49% risk reduction in CHF-related death. No difference was seen with respect to benefit based on etiology, although slightly greater benefit was seen in patients with CHF of ischemic etiology. Similar benefit was seen in patients with previous myocardial infarction (MI), diabetes mellitus, and a previous history of hypertension. Male patients appeared to derive greater benefit than female patients.

Table 1: Results of MERIT-HF

	Metoprolol N=1,990	Placebo N=2,001
Age (years)	64	64
% Male	77%	78%
NYHA II	41%	41%
III	56%	55%
IV	3.5%	3.0%
Etiology		
Ischemic	65%	66%
Non-ischemic	35%	34%
Co-treatment		
ACE inhibitors	89%	90%
Angiotensin II inhibitors	7%	6%
Diuretics	91%	90%
18-month mortality	17.2%	11.0% p=0.0062 (adjusted)

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Table 2: FRISC II mortality + infarction at 90 Days		
Randomized	**Conservative**	**Invasive**
Placebo	12.7% n=600	9.8% n=599
Dalteparin	11.5% n=610	9.2% n=599

FRISC II: LMWH (dalteparin) in acute coronary syndromes

This multicentre, international study investigated the potential benefit of dalteparin (Fragmin) — a low-molecular weight heparin (LMWH) — in patients with unstable angina or non-Q-wave MI. The study design was complex, but included initial treatment with 120 IU/kg twice daily of all patients for the first week. After the initial 48 hours, patients were randomized to either an invasive treatment strategy that included coronary angiography and revascularization, or a medical treatment arm. Each of the treatment arms, invasive and conservative, had re-randomization of patients to either long-term administration of subcutaneous dalteparin or placebo.

The important results of the study are as follows. Six-month death and MI incidence were significantly reduced in 11,090 patients randomized to the invasive strategy (9.5%), compared to that seen in 12,014 patients randomized to the conservative strategy (12.0%, p=0.045). Death alone was also reduced, but insignificantly (1.9% vs 3.0%, p=0.10).

Table 3: Safety and efficacy of TNK-tPA (ASSENT II Study)			
	TNK-tPA N=8,462	**tPA N=8,488**	**p value**
30-day mortality	6.17%	6.15%	NS
Intracranial hemorrhage (ICH)	0.93%	0.93%	NS

Interestingly, men appeared to derive a particular benefit from the invasive strategy with six-month death and MI incidence being significantly lower in the invasive arm (9.1% vs 13.9%, p=0.002). Even more impressive, death alone was significantly reduced at six months in 822 men randomized to invasive strategy, compared to 844 men randomized to conservative strategy (1.5% vs 3.2%, p=0.03).

With respect to the efficacy of long-term administration of dalteparin, no difference was seen in 90-day incidence of death and infarction when open and double-blind administration of dalteparin was included (10% vs 11.1%, p=0.45). Table 2 demonstrates a more detailed result of 90-day com-

Table 4: Safety and efficacy of nPA (InTime-II)			
	nPA N=10,051	**tPA N=5,027**	**p value**
30-day mortality	6.77%	6.60%	NS
ICH	1.13%	0.62%	0.003

Table 5: 30-day analysis				
	Placebo	**Orbo 50/30**	**Orbo 50/50**	**p value (Each treatment arm vs placebo)**
Composite	10.7	9.7	9.3	0.14/0.05
Death	1.4	2.3	1.6	0.004/0.53
MI	3.1	3.0	2.6	NS
Urgent revasc.	5.2	2.9	3.3	<0.0001
Rehospitalization	4.1	4.0	4.0	NS
Stroke	0.5	0.5	0.6	NS

Table 6: End of follow-up analysis (300 days)				
	Placebo	Orbo 50/30	Orbo 50/50	p value (Each treatment arm vs placebo)
Composite	20.5	20.2	19.5	NS
Death	3.2	4.7	4.0	0.001/0.06
MI	4.8	4.9	5.4	NS
Urgent revasc.	7.9	5.9	5.8	0.002/0.004
Rehospitalization	11.8	11.9	10.9	NS
Stroke	0.9	1.0	1.1	NS

parison based on randomization. There was a slight increase in bleeding observed with dalteparin therapy.

In summary, long-term (90-day) administration of dalteparin is not warranted based on the results of FRISC II. These observations support the previously reported results of TIMI 11B that demonstrated no additional benefit from long-term (after 42 days) administration of enoxaparin in patients with unstable angina and non-Q-wave MI.

Thrombolytic therapy: ASSENT II and InTime-II Studies

A more complete description of these two studies appears in a *Cardiology Scientific Update* specifically dedicated to these two studies. Tables 3 and 4 summarize the most important safety and efficacy data.

These studies indicate that single bolus administration of either TNK-tPA or lanoteplase (nPA) is associated with a similar reduction in 30-day mortality compared to an accelerated regimen of tPA in patients with acute MI. The greater occurrence of intracranial hemorrhage observed with nPA raises safety concerns. TNK-tPA appears to be as safe as tPA with respect to intracranial hemorrhage and may offer further reduction in bleeding complications (non-ICH minor bleeding) in relation to its greater fibrin specificity.

Update on IIb/IIIa Therapy: The OPUS, EXCITE and EPISTENT Trials

OPUS: Orbofiban (oral IIb/IIIa) in acute coronary syndromes

Patients with acute coronary syndromes were enrolled within 72 hours and randomized to either placebo or orbofiban given either as 50 mg twice a day for the first month followed by 30 mg twice a day thereafter, or as a 50 mg twice a day regimen throughout. Primary efficacy endpoints

Table 7: Bleeding events (300 Days)				
	Placebo	Orbo 50/30	Orbo 50/50	p value (Each treatment arm vs placebo)
Severe	0.4	1.2	0.7	0.0001/0.04
ICH	0.1	0.2	0.1	NS
Major	1.7	2.2	3.1	NS
Major/severe	1.9	3.3	3.7	<0.001
Platelets 50,000 – 80,000	0.1	0.6	0.6	
Platelets <50,000			0.3	

Table 8: Xemilofiban in patients undergoing PCI (EXCITE)

	Placebo	Xemilofiban 10 mg tid	Xemilofiban 20 mg tid
One month death + MI	6.5%	6.5%	5.8%
Six month death + MI	9.8%	10.2%	8.9%

were death, MI, recurrent ischemia, urgent revascularization, and stroke. The study stopped enrollment in early November 1998 and stopped drug administration in mid-January 1999. Tables 5-7 summarize incomplete data available to-date and indicate some evidence of benefit with respect to primary endpoint at 30 days, but not beyond. Also, there is a disturbing increase in mortality that has not been explained. An increase in bleeding (Table 7) is also seen.

EXCITE: Xemilofiban (oral IIb/IIIa) in PCI

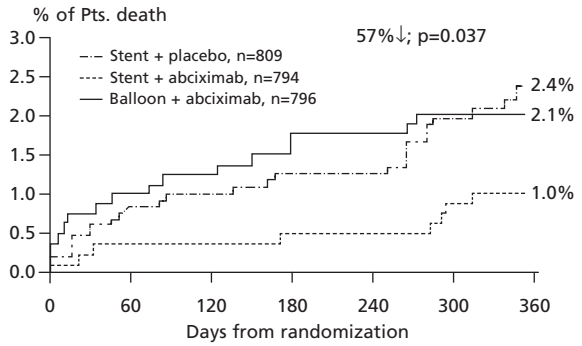
All comers undergoing percutaneous coronary intervention (PCI) (n=7,246) were randomized to either placebo, xemilofiban 10 mg tid, or xemilofiban 20 mg tid, and followed for six months. Among patients enrolled, 45% had unstable angina, 43% had stable angina, and 13% had acute MI. No difference in primary event rate of death or MI was seen in either of the treatment groups (Table 8).

Interestingly, significant benefit with respect to xemilofiban treatment was seen in patients with diabetes mellitus.

EPISTENT: Abciximab and PTCR

A one-year follow-up of the EPISTENT Study was presented (Figure 1) demonstrating significant reduction in major coronary events, including mortality, in association with strategy the combines stent and abciximab administration.

Figure 1: EPISTENT Mortality at 1 year – ITT patients



Conclusion

This brief overview of some recently presented clinical trials supports the use of beta-blockers, and in particular metoprolol, in patients with CHF. There is now evidence that an interventional approach in patients with acute coronary syndromes may be associated with a better outcome than a conservative strategy. Finally, our understanding of IIb/IIIa antiplatelet strategy moves to yet another level with great news regarding the combination of stent and abciximab on one hand, and uncertainty with respect to oral treatment on the other with the results of EXCITE and OPUS studies.