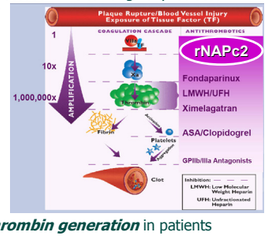
Safety and Tolerability of a Novel Tissue Factor / Factor VIIa Inhibitor rNAPc2 in Patients with NSTE-ACS Managed Invasively: Results from the ANTHEM-TIMI 32 Trial

Richard G. Bach, Robert P. Giugliano, Daniel I. Simon, Marc J. Schweiger, Massoud A. Leesar, Stephen D. Wiviott, Michael A. Goulder, Steven R. Deitcher, Eugene Braunwald; Washington University Medical Center, St. Louis, MO, Brigham and Women's Hospital, Boston, MA

INTRODUCTION

Despite intensive antiplatelet, anticoagulant, and anti-ischemic therapy, and early invasive management, recurrent MI or death remain frequent events among high-risk patients with non-ST-elevation acute coronary syndrome (nSTE-ACS). In patients with ACS, plaque rupture and PCI expose **tissue factor** that can rapidly generate thrombin and activate coagulation. Current standard antithrombotic therapies (heparin, aspirin, clopidogrel, glycoprotein (GP) IIb/IIIa blockers) **do not adequately suppress thrombin generation.**

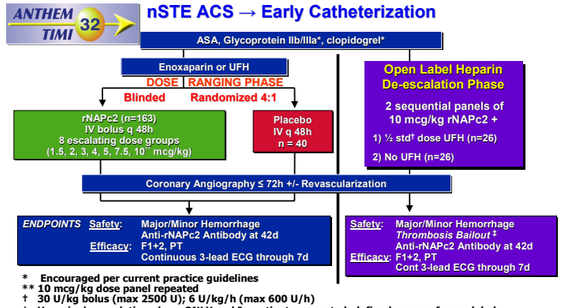
Recombinant nematode anticoagulant protein c2 (**rNAPc2**) is an 85-amino acid serine protease inhibitor originally isolated from the hookworm parasite *Ancylostoma caninum*. The anticoagulant activity results from **inhibition of the catalytic complex of factor VIIa/tissue factor (fVIIa/TF)** by a unique mechanism. The elimination half-life is estimated to be 50-60 hours in man.
Prior studies of rNAPc2 have demonstrated its novel potential to ***inhibit thrombin generation*** in patients undergoing ***elective*** PCI.



STUDY PURPOSE

The goal of ANTHEM-TIMI 32 was to evaluate safety (and efficacy) of a range of doses of rNAPc2 in patients with nSTE-ACS managed with standard therapies including early invasive strategy.

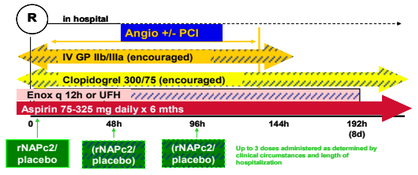
STUDY DESIGN:



* Encouraged per current practice guidelines
** 10 mcg/kg dose panel repeated
† 30 U/kg bolus (max 2500 U); 6 U/kg/h (max 600 U/h)
‡ Heparin de-escalation phase ONLY and Investigator reported; defined as use of open-label anticoagulant to manage thrombotic complication
Note: The incidence of procedure-related thrombosis was prospectively collected in the open label heparin de-escalation phase only, and not among the 203 patients in the dose-ranging phase of the study.

ENTRY CRITERIA AND STUDY SCHEMA:

Inclusion: Age 18-75, rest sx ≥ 5min w/i 48h c/w ACS
+ markers or ST deviation or TIMI Risk Score ≥ 3
Planned early invasive strategy
Exclusions: STEMI, creatinine > 4, ↑bleed risk, planned CABG <7d



RESULTS

Table 1. Baseline Characteristics and Treatments

	rNAPc2 n = 215	placebo n = 40	P-value
Age (median), yrs	58	56	NS
Age ≥ 65 yrs, %	28	18	NS
Women,%	34	20	NS
nSTE-MI,%	54	50	NS
STdev>0.5mm,%	47	45	NS
Diabetes,%	34	33	NS
Mean TIMI Risk Score	3.7	4.0	NS
#Study Drug Doses 1/2/3,%	83/18/2	83/18/0	NS
*Enoxaparin/UFH,%	71/33	75/33	NS
Clopidogrel,%	81	85	NS
GP IIb/IIIa Inhibitor,%	54	53	NS
PCI/CABG/Medical,%	48/11/41	60/3/37	NS

*Excludes 52 patients in the heparin de-escalation phase

Figure 1: Higher Dose rNAPc2 Reduced:
(A) New Thrombin Generation **(B) Ischemic Episodes**

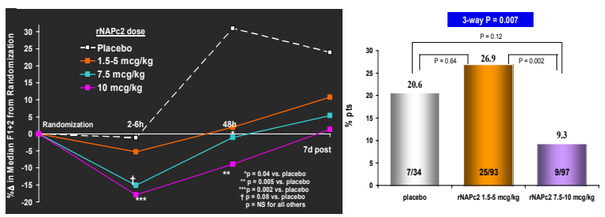


Figure 1: (A) Change in F1+2, a marker of new thrombin generation, from baseline by treatment group and time; rNAPc2 at 10 and 7.5 mcg/kg significantly reduced new thrombin generation (B) Incidence of recurrent in-hospital ischemia by ST shifts on continuous ST segment monitoring was significantly reduced by rNAPc2 at 7.5-10 mcg/kg .

Table 2. Bleeding Outcomes, rNAPc2 vs. Placebo

	rNAPc2 n = 215	placebo n = 40	P-value
TIMI Major, n(%)	4(1.9)	0(0.0)	NS
Non-CABG TIMI Major	1(0.5)	0(0.0)	NS
TIMI Minor	4(1.9)	1(2.5)	NS
TIMI Major or Minor	8(3.7)	1(2.5)	NS
Any Reported Bleed*	28(13.0)	5(12.5)	NS
RBC Transfusion	14(6.5)	1(2.5)	NS
Ave # PRBC Transfused	2.2	2.0	NS
Fresh Frozen Plasma	2(0.9)	1(2.5)	NS
Thrombocytopenia ‡	3(1.4)	0(0.0)	NS
Platelet Transfusion	1(0.5)	1(2.5)	NS
Recombinant FVIIa	0	0	--
αrNAPc2 Ab+ @ 42d	23(13.0)†	0(0.0)	0.03

*Note: All major/minor bleeds were provoked by procedure/trauma as were 79% of the minimal bleeds
‡ Platelet counts of 99K, 98K, and 93K.
† % based on available data; No cases of allergic symptoms or anaphylaxis were reported

Figure 2: Adjudicated Bleeding by Anti-Thrombotic Medication Doses

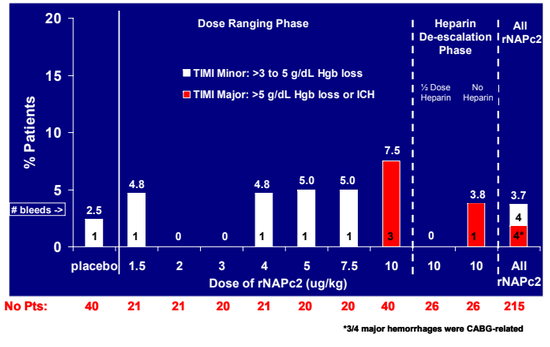


Table 3. Events According to Anti-Thrombotic Medication Doses

	rNAPc2 <10 mcg/kg n = 123	rNAPc2 10 mcg/kg+ Full dose hep n = 40	rNAPc2 10 mcg/kg+ ½ dose hep n = 26	rNAPc2 10 mcg/kg+ no heparin n = 26	placebo n = 40	P-value (5-way)
TIMI Major, n(%)	0(0.0)	3(7.5)	0(0.0)	1(3.8)	0(0.0)	0.011
Non-CABG TIMI Major	0(0.0)	1(2.5)	0(0.0)	0(0.0)	0(0.0)	NS
TIMI Minor	4(3.3)	0(0.0)	0(0.0)	0(0.0)	1(2.5)	NS
TIMI Major or Minor	4(3.3)	3(7.5)	0(0.0)	1(3.8)	1(2.5)	NS
Any Reported Bleed*	14(11.4)	8(20.0)	3(11.5)	3(11.5)	5(12.5)	NS
RBC Transfusion	6(4.9)	5(12.5)	0(0.0)	3(11.5)	1(2.5)	NS
Mean Peak PT	21.62±7.4	34.2±13.5	29.9±9.2	22.6±8.2	17.2±3.8	<0.0001
Procedure-related thrombosis‡	--	--	0	4(15)	--	0.051‡
αrNAPc2 Ab+ @ 42d†	11(11.2)	4(11.4)	5(20.8)	3(11.5)	0(0.0)	NS

*Note: All major/minor bleeds were provoked by procedure/trauma as were 79% of the minimal bleeds
‡Thrombosis prospectively collected only in open-label heparin de-escalation phase; p-value for "no heparin" vs. "½ dose" group; 1 additional pt in the "no heparin" group reported to have recurrent ischemia prior to cath that required bailout anticoagulation (UFH).
† % based on available data; No cases of allergic symptoms or anaphylaxis were reported

SUMMARY

- rNAPc2 caused a dose-related increase in PT (Table 3); doses ≥7.5 mcg/kg were associated with a significant reduction of new thrombin generation at 2-6 and 48h (Figure 1A) and with a significant >50% reduction in the incidence of ischemic episodes by continuous ECG (Figure 1B).
- rNAPc2 was generally well tolerated; there were 8 significant hemorrhages (3.7%), including 4 major and 4 minor, among the 215 patients receiving rNAPc2 in the trial (p=NS vs. placebo, Table 2).
- All 4 major hemorrhages occurred at highest dose (10 mcg/kg) and were procedure-related (3/4 CABG-related, 1 cath access site). Shorter interval between the last dose of rNAPc2 and CABG was associated with a trend toward higher bleeding risk (40% vs 10% vs 0% for CABG performed <48h vs 48-96h vs. >96h, trend p=0.077). Bleeding was associated with CABG <96h after last dose of drug, but not anticoagulant type, use of clopidogrel, aspirin dose, or IIb/IIIa inhibitor use.
- Other safety outcomes, including rates of other (neither major nor minor) bleeding (9.8% vs 10%), frequency of transfusion (6.5% vs 2.5%), average # of units transfused (2.2 vs 2.0), and serious adverse events (30% vs 33%) were similar between rNAPc2 and placebo (all p = NS). No patients required treatment with activated FVII concentrate to reverse rNAPc2 anticoagulation.
- Anti-rNAPc2 antibody was detected at 42 days in 13% of patients receiving rNAPc2; no patient had an allergic reaction or anaphylaxis; there were no differences in clinical outcome or pharmacodynamic effects among patients who were + vs – for antibody.
- In the open-label heparin de-escalation phase, investigators reported 4(15%) procedure-related thromboses (and 1 episode of recurrent ischemia prior to cath) in the no heparin group and none with half-dose heparin.

CONCLUSIONS:

1. In NSTE-ACS patients managed invasively, TF targeted inhibition of thrombin generation by rNAPc2 reduced ischemia without a significant increase in non-CABG bleeding.
2. rNAPc2 was associated with a moderate incidence (13%) of anti-rNAPc2 antibody at 42 days, not associated with clinical sequelae.
3. Adjunctive heparin or inhibitors of the terminal portion of the coagulation cascade at PCI may reduce the risk of procedural thrombosis.
4. These data suggest favorable safety of rNAPc2, requiring confirmation in larger scale clinical trials.