30 Day Morbidity and Mortality Associated with Endovascular Treatment of Intracranial Aneurysms

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Clinical Data

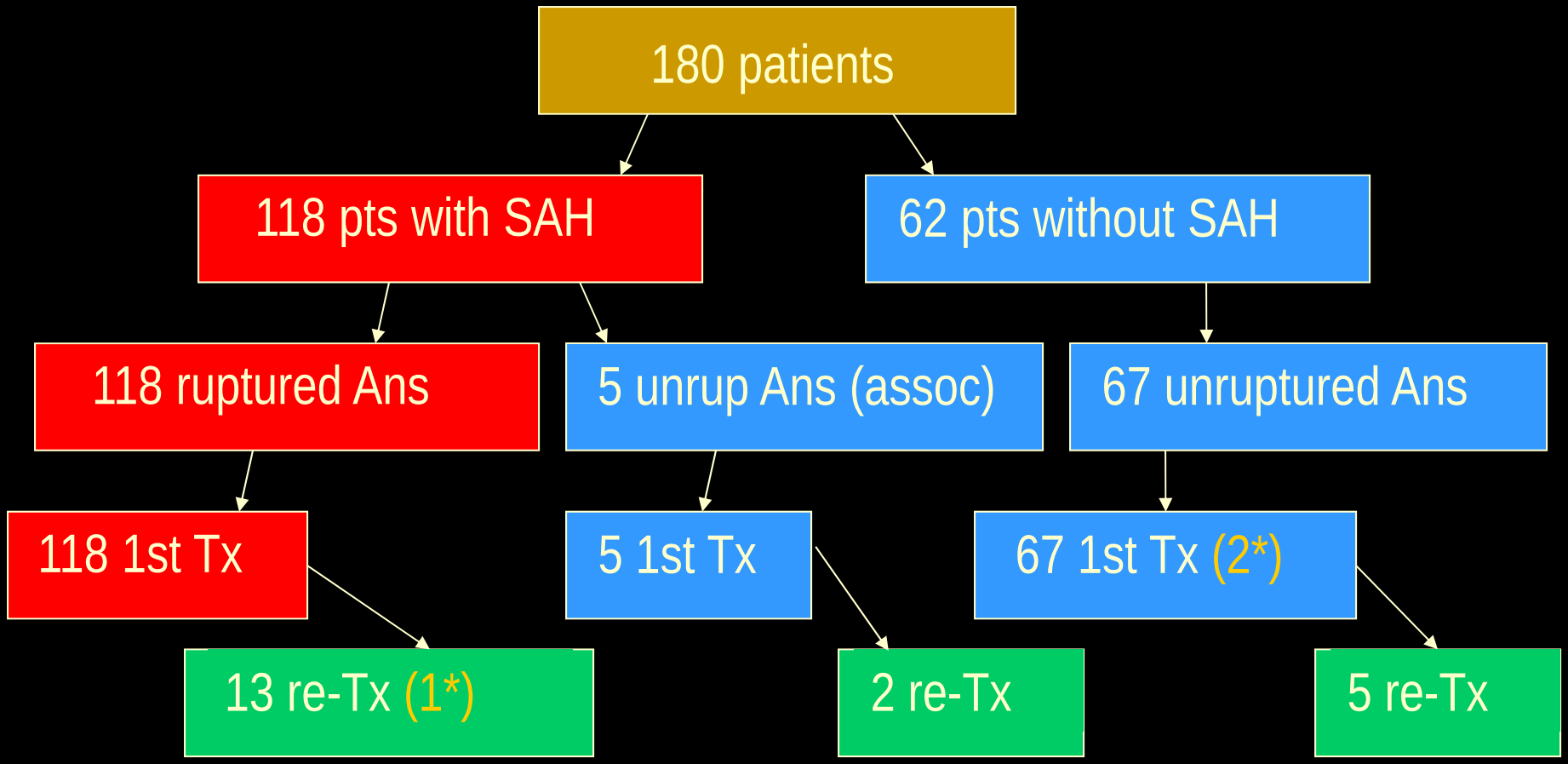
- Oct 1998 - Oct 2002 (49 mo)
- 180 pts (118 with SAH, 62 without SAH)
  - M:F 50(27.8%):130(72.2%)
  - Ages 25-91 yrs (mean, 56.9 yrs)
  - Of 118 pts with SAH
    - 22 HH I
    - 25 HH II
    - 36 HH III
    - 30 HH IV
    - 5 HH V
- 190 aneurysms (118 ruptured, 72 unruptured)

Clinical Data

- 210 procedures (including 3 failures)
- 118 ruptured aneurysms
  - 114 treated within 72 hrs
  - 4 treated after 72 hrs
- 72 unruptured aneurysms treated electively.
- Only 1 aneurysm treated per procedure.

Clinical Data

180 patients, 190 aneurysms, 210 procedures



* technical failure

Clinical Data

- Cases in which cerebral complications occurred **during their admission periods** were selected.
- Radiologic findings, clinical presentations, treatments, and outcomes were analyzed.

Aneurysm Location

	Ruptured	Unruptured
Anterior circulation	88 (74.6%)	53 (73.6%)
AchA	4	2
PcoA	13	4
Paraclinoid ICA	7	32
ICA bifurcation	5	2
A1	1	1
AcoA	45	6
distal ACA	6	1
M1	1	0
MCA bifurcation	6	5
Posterior circulation	30 (25.4%)	19 (26.4%)
BA tip	16	11
Distal PCA	3	1
SCA	2	3
BA	1	1
VBJ	1	0
PICA	7	3
Total	118	72

Aneurysm Size

Size (mm)	Ruptured	Unruptured	Total (%)
Small ≤10	93	52	145 (76.3%)
Large 11-24	23	20	43 (22.6%)
Giant ≥ 25	2	0	2 (1.1%)
Total	118	72	190

Fundus/Neck Ratio

- 118 ruptured aneurysms
  - 45(38.1%) >2
  - 73(61.9%) ≤2
- 72 unruptured aneurysms
  - 21 (29.2%) >2
  - 51(70.8%) ≤2

Radiographic Results of Initial Embolizations

	Ruptured	Unruptured
Complete	74 (62.7%)	42 (58.3%)
Near-complete	25 (21.2%)	17 (23.6%)
Partial	19 (16.6%)	11 (15.3%)
Failure	0	2 (2.8%)
Total	118	72

Average Hospitalization Period

- Patients with acutely ruptured aneurysms
  - without procedural & SAH-associated complications: 12.9 days
  - with procedural complications: 10.2 days (artificially reduced due to mortalities)
  - with SAH-associated complications: 25.5 days
- Patients with unruptured or retreated aneurysms
  - without procedural complications: 3.6 days
  - with procedural complications: 7.5 days

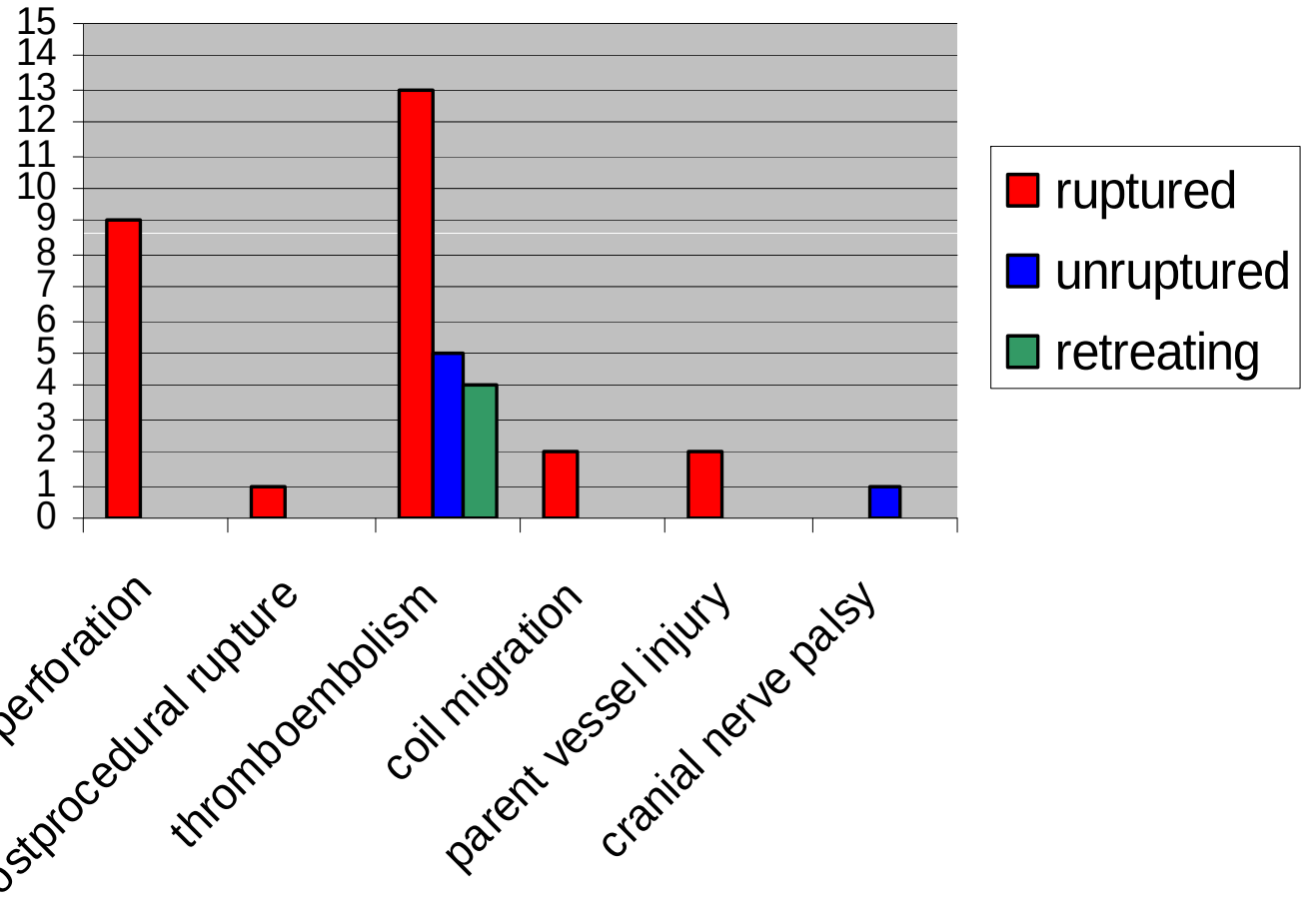
Procedural Complications
(Total of 210 Procedures)

Total Complications	37	17.6%
Complications:		
cerebral thromboembolism	22	10.4%
aneurysm perforation	9	4.2%
coil migration	2	1%
parent vessel injuries	2	1%
postprocedure an rupture	1	0.5%
cranial nerve palsy	1	0.5%

Procedural Complications
(For a Total of 210 Procedures)

Procedural Compliction	Neurologic Sequelae				Total	Incidence rate/210 procedure
	No	Transient after procedure	Persistent on discharge	Resulting in death		
Perforation	6	0	0	3	9	4.2%
Postprocedural rupture	0	0	0	1	1	0.5%
Thromboembolism	5	2	10	5	22	10.4%
Coil migration	1	0	0	1	2	1.0%
Parent vessel injury	2	0	0	0	2	1.0%
CNP	0	1	0	0	1	0.5%
Total	14	3	10	10	37	17.6%

Complications (n=37)
In 210 Procedures



Procedural Morbidity & Mortality (For 210 Procedures)

- 14 comps resulted in no neurologic consequence (38% of complications; 6.6% of entire group)
- 3 comps resulted in transient neurologic deficit (8% of complications; 1.4% of entire group)
- 10 comps resulted in persistent neurologic deficit (27% of complications; 4.7% of entire group)
- 10 comps resulted in death (27% of complications; 4.7% of entire group)
- Overall procedure-related neurologic morbidity and mortality rates were 9.6% total (20/210)

Procedural Morbidity & Mortality (For 210 Procedures)

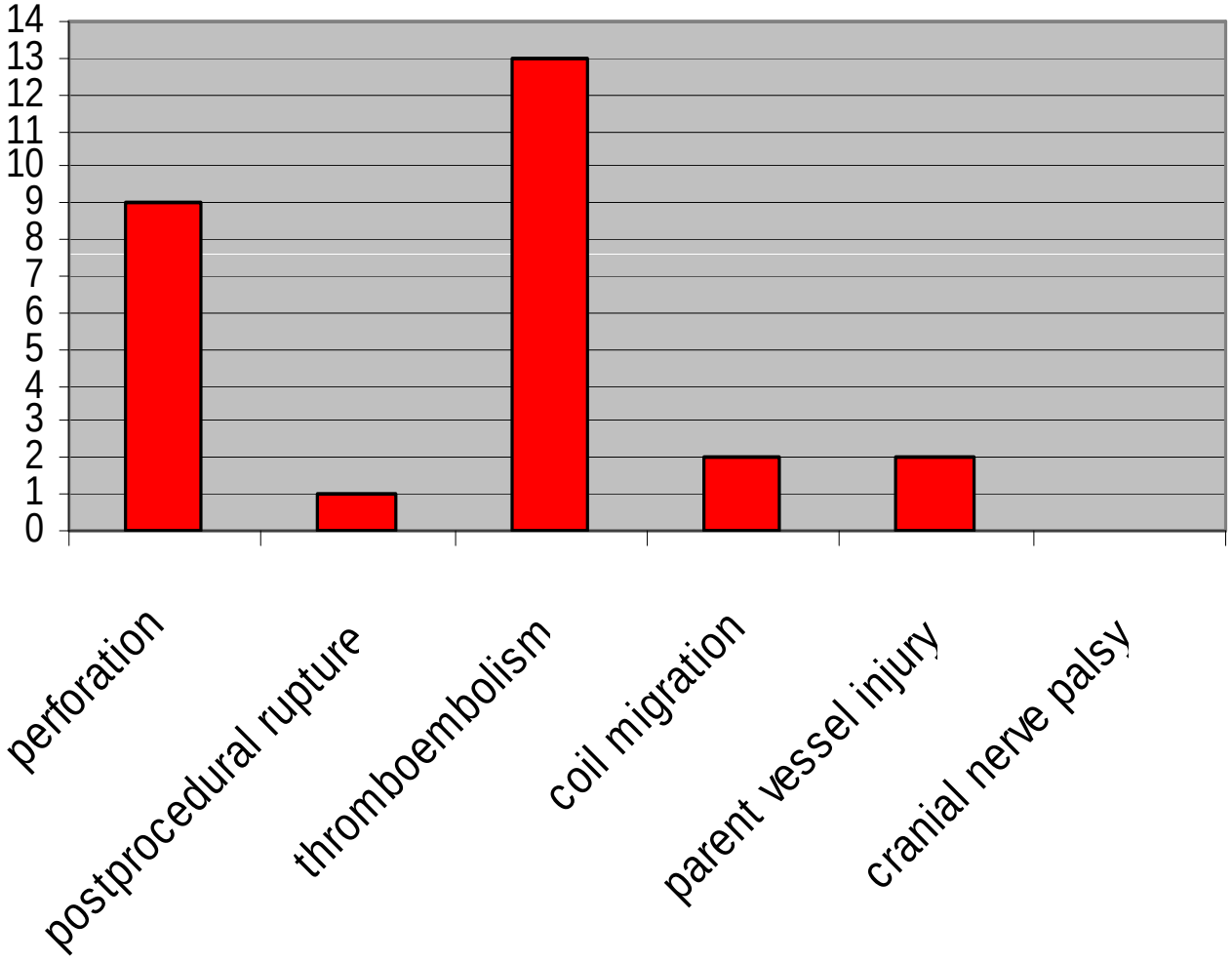
Complication rate	37/210	17.6%
Morbidity	10/210	4.8%
Mortality	10/210	4.8%

Procedural Complications

(For 118 ruptured aneurysms)

Procedural Complication	Neurologic sequelae				Total	Incidence rate/118 procedures
	No	Transient after procedure	Persistent on discharge	Leading to death on discharge		
Intraprocedural rupture	6	0	0	3	9	7.6%
Postprocedural rupture	0	0	0	1	1	0.8%
Thromboembolism	1	1	7	4	13	11.0%
Coil migration	1	0	0	1	2	1.7%
Parent vessel injury	2	0	0	0	2	1.7%
Total	10	1	7	9	27	22.9%

Complications of 118 Ruptured Aneurysms (n=27)



Procedural Morbidity & Mortality (For ruptured aneurysms)

Complication rate	27/118	22.9%
Morbidity	7/118	5.9%
Mortality	9/118	7.6%

Nonprocedural Complications of SAH

	No. of Patients (No. of death on discharge)
Rebleeding	1 (1)
Vasospasm managed by HHH, intraarterial papaverine or angioplasty	7 (1)
Hydrocephalus shunted	7 (0)
Total	14 (2)

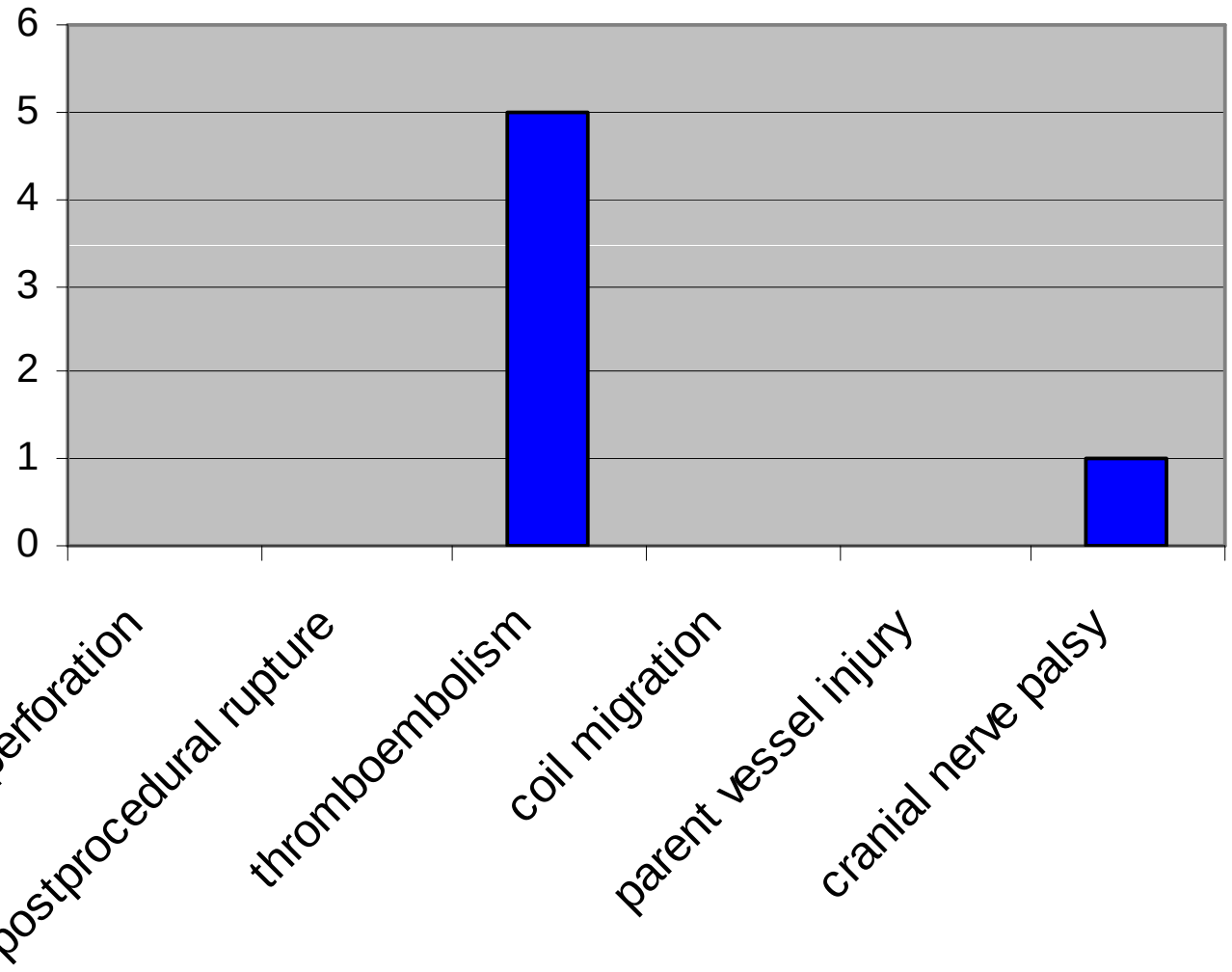
Prevalence of Complications of SAH		
Early rebleeding	1/118	0.9%
Vasospasm	7/118	5.9%
Hydrocephalus	7/118	5.9%

Causes of Mortality from Complications of SAH		
Initial impact of SAH	12/118	10.2%
Early rebleeding	1/118	0.85%
Vasospasm	1/118	0.85%
Total	14/118	11.9%

Procedural Complications
(For 72 unruptured aneurysms)

Procedural Complication	Neurologic sequelae				Total	Incidence rate/72 procedures
	No	Transient after procedure	Persistent on discharge	Leading to death on discharge		
Thromboembolism	2	1	1	1	5	6.9%
Cranial nerve palsy	0	1	0	0	1	1.4%
Total	2	2	1	1	6	8.3%

Complications of 72 Unruptured Aneurysms (n=6)



Procedural Morbidity & Mortality (For unruptured aneurysms)

Complication rate	6/72	8.3%
Morbidity	1/72	1.4%
Mortality	1/72	1.4%

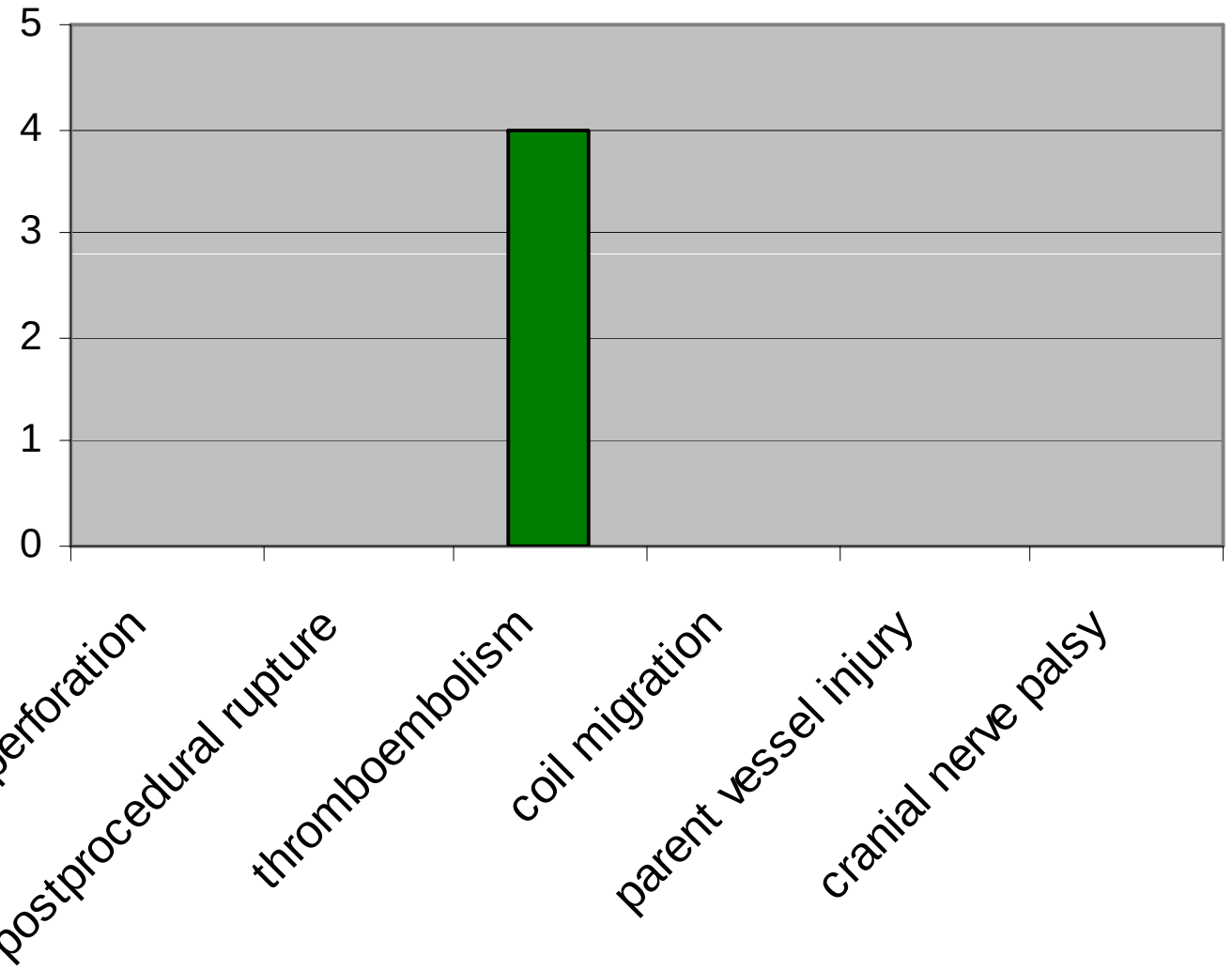
Procedural Complications
(For 20 reembolizations)

- No. of reembolization: 20 (14 aneurysms reembolized once, 2 reembolized 3 times)
- Of 20 reembolization, 4 (20%) were complicated: all 4 complications were thromboembolic.

Procedural Complications
(For 20 reembolizations)

Procedural complication	Neurologic sequelae				Total	Incidence rate/20 procedures
	No	Transient after procedure	Persistent on discharge	Leading to death on discharge		
Thromboembolism	2	0	2	0	4	20%

Complications of 20 Reembolizations (n=4)



Procedural Morbidity & Mortality (For reembolization)

Complication rate	4/20	20%
Morbidity	2/20	10%
Mortality	0/20	0%

Summary of Complication /Morbidity /Mortality Rates

	Total Procedures (n=210)	Ruptured aneurysm (n=118)	Unruptured aneurysm (n=72)	Retreated aneurysm (n=20)
Complication	17.6%	22.9%	8.3%	20%
Morbidity	4.8%	5.9%	1.4%	10%
Mortality	4.8%	7.6%	1.4%	0%

- Complication rate: highest in ruptured group, lowest in unruptured group
- Morbidity rate: highest in retreated group, lowest in unruptured group
- Mortality: higher in ruptured group than in unruptured group

Reported Complication Rate of EVT of Aneurysms

	No. of aneurysms treated		Procedural complication rate	Morbidity	Mortality
	Ruptured	Unruptured			
Raymond and Roy, 1997	75	0	23%	4%	4%
Vinuela et al, 1997	403	0	9.18%	8.9%	1.74%
Kuether et al, 1998	31	46	14%	9.1%	7.8%
Roy et al, 2001	0	125	10.3%	4.3%	0%
Ng et al, 2002	81	59	21%	6.9%	1.2%
Our series	**118**	**72**	**17.6%**	**4.8%**	**4.8%**

Aneurysm Perforation

- 9/210 (4.2%)
  - Indicated by protrusion of the coil (6) or the microcatheter (3) outside the limit of aneurysmal sac
  - Contrast extravasation: (+) in 7, (-) in 2
  - All occurred during the early stage (before detachment of the halfway coil) of the procedure.

Aneurysm Perforation

- All aneurysms perforated were previously ruptured
  - 7.6% of 118 ruptured aneurysms

Aneurysm Perforation

- HH grade
  - I: 1/22 (4.5%)
  - II: 2/25 (8%)
  - III: 3/36(10%)
  - IV: 3/30 (10%)
- Location
  - AChA: 1/6 (16%)
  - MCA: 1/12 (8.3%)
  - B-tip: 1/27 (3.7%)
  - B-trunk:1/2 (50%)
  - A-com: 4/51(7.8%)
  - VBJ: 1/1 (100%)
- Size
  - small: 8/9 (89%)
  - large: 1/9 (12%)

Aneurysm Perforation

- Inherent limits to precise control of coils and microcatheters will pose risks of perforation.
- Incidence of occurrence of aneurysmal perforation was sporadic in our series.

Aneurysm Perforation

	Number of Aneurysms Treated		Number of Aneurysms Perforated
	Total	Ruptured	
1998	1	0	0
1999	22	13	1(5%)
2000	50	24	1(2%)
2001	79	48	2 (3%)
2002	58	33	5 (9%)
Total	210	118	9 (4.2%)

Aneurysm Perforation

(For ruptured aneurysms)

- Management
  - protamine injection
  - continuing coil deployment; introduce second catheter for coiling before removing first catheter from hole
  - EVD: 3 inserted after perforation, 5 placed before coiling (timing of EVD placement often determined by neurophysiology findings)
- Outcome
  - 6 had no sequelae
  - 3 resulted in death

Aneurysm Perforation

- Morbidity/Mortality from aneurysm perforation
  - 118 ruptured aneurysms: 0% 2.5%
  - 210 total procedures: 0% 1.4%
- All 3 deaths were associated with intraprocedural perforations during placement of first coil (high pressure/high volume bleeds)
- All 3 deaths had poor initial Hunt-Hess Grades (HH 3, 4, 4)

Aneurysm Perforation; Literature Review

- Reported rate of aneurysm perforation
  - 1.9-16% for ruptured aneurysms (2-9% our series)
  - 0-1.3% for unruptured aneurysms (0% our series)
- Occurred almost invariably among ruptured aneurysms (100% in our series)
- Small aneurysm - higher incidence of perforation (89% in our series)
- Outcome: either fatal or good (33% fatal/66% good in our series)

Thromboembolism

- Observed in 22 (10.4%) of a total of 210 procedures
  - 11% of ruptured aneurysms
  - 6.9% of unruptured aneurysms
  - 20% of retreated aneurysms
- Reported rates: 2.5% - 28%
- Accounted for **59.5%** of all complications in this series

Thromboembolism

- Morbidity/Mortality from thromboembolism in 210 procedures: 4.8%/2.4%
  - Thromboembolism responsible for 100% of the series' morbidities
  - Thromboembolism responsible for 50% of the series' mortalities

Thromboembolism

- Thromboembolic complications
  - during the procedures (12 cases)
  - within 24 hours of the procedures (10 cases).
- Management
  - fibrinolytics (IA tPA in 1 case)
  - antiplatelet agents (IA or systemic IIb/IIIa inhibitors in 8 cases)

Thromboembolism

- Our present approach (since Nov. 2002) to decrease the incidence of thromboembolic complication includes the preventive use of bolus IV Eptifibatide (Integrilin) +/- IV infusion at the end of the procedure to reduce the postprocedural thromboembolic complication rate.

Thromboembolism

- Eptifibatide was used in 28 out of 42 EVT for intracranial aneurysms (11/4/2002-4/14/03)
  - intraprocedural use: 2
  - used at the end of procedures: 26
  - 4 thromboembolic complications occurred
    - 2 during procedure
    - 2 after procedure (2/26) despite Integrelin (7.6%)
      - 10/198 prior to Integrelin (5.1%)
  - 1 retroperitoneal hm (? transfusion need)

Hydrocephalus after EVT of Ruptured Aneurysm

- Literature Incidence of hydrocephalus after SAH 6-67%.
  - Cooperative Study — 8.0% shunting
  - In our series — 5.9% shunting

Vasospasm after EVT of Ruptured Aneurysm

- Symptomatic vspasm reported in 22-40% of patients with SAH.
- Murayama et al., 1997
  - incidence of symptomatic vasospasm after EVT of acutely ruptured aneurysms:23%
  - concluded that this rate compared favorably with that in surgical series.

Vasospasm after EVT of Ruptured Aneurysm

- Yalamanchili 1998- symptomatic vspasm:
  - 14/19 surgically treated group (73%)
  - 4/18 endovascularly treated group (22%)
- Charpentier 1999- symptomatic vspasm:
  - 22% of patients in craniotomy group
  - 17% in the endovascular treatment group

Vasospasm after EVT of Ruptured Aneurysm

- In our series
  - symptomatic vasospasm 5.9%
  - results indicate that EVT may be associated with a reduced incidence of symptomatic vasospasm in patients with acutely ruptured aneurysm (consistent with those of some earlier reports).

Conclusion

- Endovascular therapy for aneurysms is a relatively safe procedure with :
  - 17.6% overall clinical complication rate
  - 4.8% neurologic morbidity
  - 4.8% mortality
  - 1.1% (3/271) early and late rebleed rate
  - 5.9% shunted hydrocephalus rate
  - 5.9% vasospasm rate (? missed)

Rationale for blockade of GPIIb/IIIa receptors

- Platelet thrombus formation is the dominant initiating factor.
- GPIIb/IIIa is the final common pathway leading to platelet aggregation.
- Patients lacking GPIIb/IIIa receptor function (Glanzmann thrombasthenia): variably severe mucocutaneous bleeding, rarely spontaneous CNS bleeding.

Abciximab

- High cost ($1400/patient): shift toward rescue use in PCI
- >97% success in rescue use during PCI
- Higher risk of vascular access site complications, excessive bleeding if emergency surgery is to be performed within 12 hrs after administration, thrombocytopenia

Abciximab

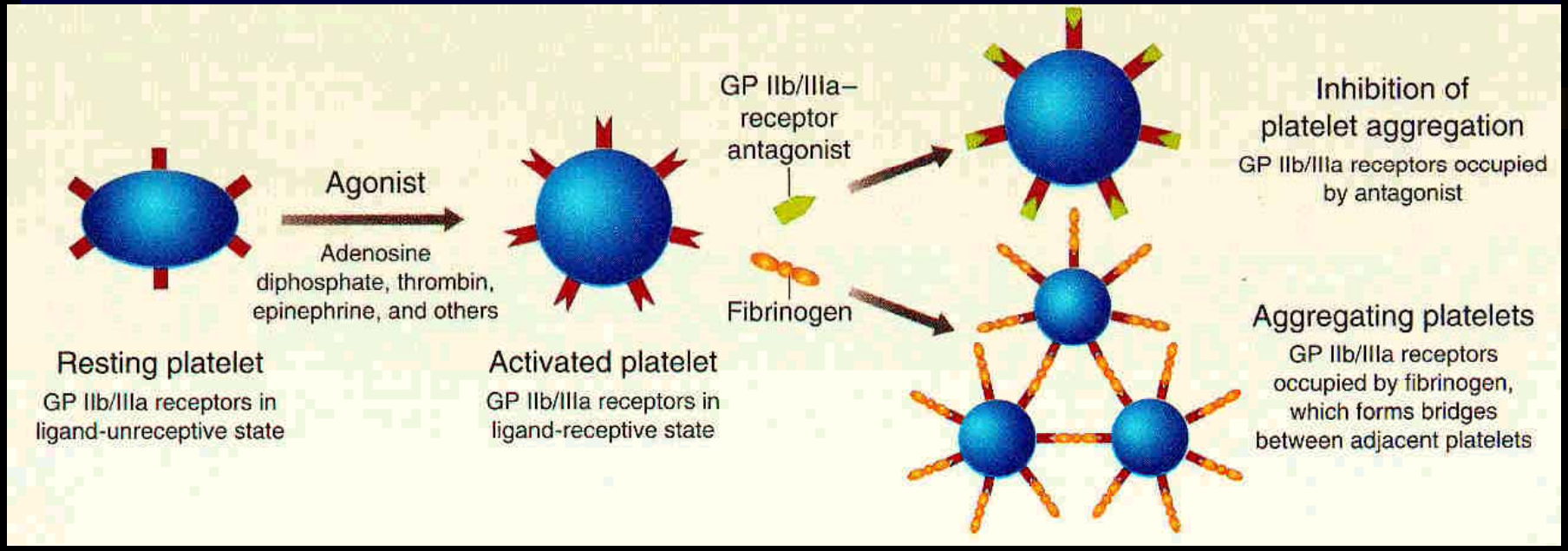
- Recovery of platelet function is slow: 29% GPIIb/IIIA receptor blockade at 8 days after administration
- Prophylactic use of abciximab during EVT of aneurysms: entails a significant risk should aneurysm perforation necessitate EVD, dangerous in patient at risk of aneurysm bleeding

GPIIb/IIIa Antagonists

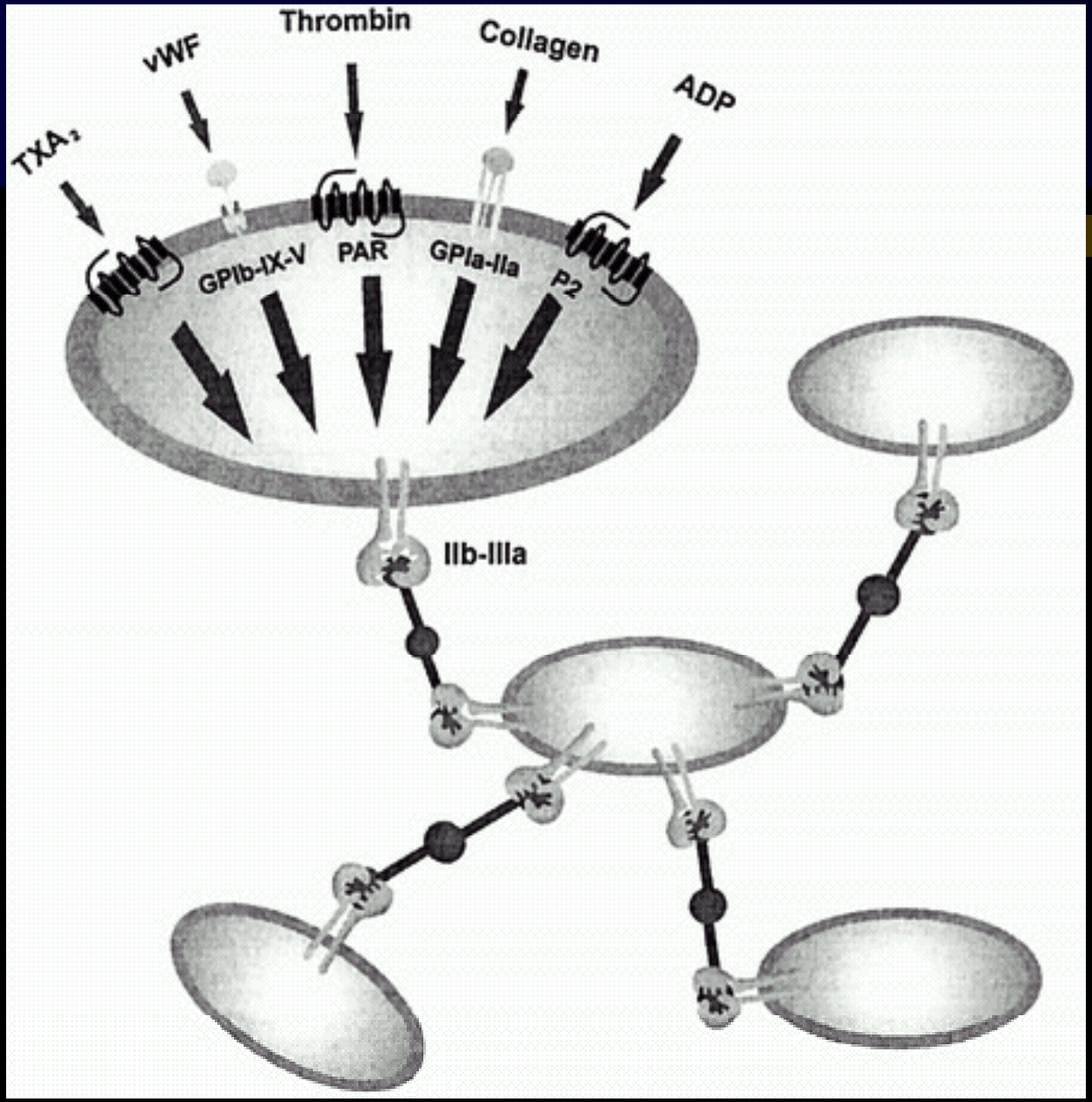
- Platelet plays an important role in acute MI, unstable angina, and ischemic stroke.
- Platelet activation→conformational changes in GPIIb/IIIa receptors on the surface of platelets → adjacent platelets are cross-linked through the bridging of activated GPIIb/IIIa receptors by fibrinogen → formation of “white” clot

GPIIb/IIIa Antagonists

- Thrombin converts fibrinogen to fibrin → stabilize white clots & entrap erythrocytes → formation of “red” clot
- Expression of GPIIb/IIIa receptors on the surface of activated platelet constitutes the final common pathway for platelet aggregation.
- GPIIb/IIIa blockade may be useful in the thrombotic disorder.



Overview of the process of platelet activation and aggregation and the inhibition of platelet aggregation by inhibitors of GP IIb/IIIa receptors


Thrombin
vWF
Collagen
ADP
TXA2
GPIb-IX-V
PAR
GPIa-IIa
P2
IIb-IIIa

Eptifibatide, Tirofiban

- Shorter half-lives than abciximab
- May be safer in patients undergoing endovascular treatment of intracranial aneurysms
- Relatively lower cost ($300-400/patient)
- >80% inhibition of platelet aggregation
  - abciximab, eptifibatide: within 10 minutes
  - tirofiban: delayed

Parenteral glycoprotein(GP) IIb/IIIa antagonists			
Feature	Abciximab (ReoPro)	Eptifibatide (Integrilin)	Tirofiban (Aggrastat)
Structure	Fab fragment of a chimeric human/mouse monoclonal Ab	Synthetic peptide	Small molecule
Molecular weight	47,615 Da	832 Da	495 Da
Mechanism of action	Irreversible antagonist of fibrinogen binding to GIIb/IIIa by steric hindrance or conformational effects	Reversible antagonist of fibrinogen binding to GPIIb/IIIa	Reversible antagonist of fibrinogen binding to GPIIb/IIIa
Cross-reactivity with other integrins	Yes	No	No
Mode of administration	IV bolus followed by continuous infusion	IV bolus followed by continuous infusion	IV bolus followed by continuous infusion
Pharmacokinetics	Plasma T1/2 ~ 10-30 mins	Plasma T1/2 ~ 2.5 hrs	Plasma T1/2 ~ 2 hrs
Platelet off-rate	Slow (~90 mins)	Rapid	Rapid
Pharmacodynamics	>80% occupancy, >80% inhibition of platelet aggregation	# 135ug/kg bolus + 0.5 ug/kg/min; 40-50% inhibition platelet aggregation at steady state, <30% inhibition platelet aggregation 4 hrs after infusion discontinuation	>90% inhibition platelet aggregation by the end of the 30-min infusion
	Platelet aggregation returns to ~50% baseline < 48 hrs after infusion discontinuation	# 180ug/kg bolus + 2 ug/kg/min; >90% inhibition platelet aggregation at steady state, <50% inhibition platelet aggregation 4 hrs after infusion discontinuation	Platelet aggregation returns to near baseline <4-8 hrs after infusion discontinuation
Elimination route	Senescent platelets	~50% renal	mostly renal
FDA-approved indications	PCI, refractory angina	PCI, ACS	ACS
FDA-approved dosing regimens	PCI: 0.25 ug/kg bolus + 0.125 ug/kg/min (max 10 ug/min) X 12 hrs	PCI: 180 ug/kg double-bolus (10 mins apart) + 2.0 ug/kg/min X 18-24 hrs	0.4 ug/kg/min X 30 mins + 0.1 ug/kg/min X 48-108 hrs; X 12-24 hrs post PCI

To reduce risk of bleeding with GPIIb/IIIa blockade

- Use low dose (70U/kg), weight-adjusted heparin, aiming for ACT of 200-300 seconds
- Discontinue heparin at the end of the procedure
- Remove vascular sheath at 4-6 hrs following the procedure, or when the ACT is below 180 seconds