rFVIIa in VAD Patients

- Limited data exist regarding safety
- Multiple factors increase pro-thrombotic potential
- Multiple case reports of successful use, with only one case report of intra-device thrombotic event
  - Reporting bias?
  - Overall incidence of thrombotic events > 20%

Summary of VAD's and rFVIIa Case Reports

Reference	Device (being implanted)	Dose of rFVIIa	Thromboembolic Event	Outcome
Apostolidou, et al.	HeartMate XVE LVAD	90 mcg/kg	LA thrombus	Recovery and OHT
Flynn, et al.	HeartMate Implantable LVAD	90 mcg/kg	None	Recovery
Heise, et al.	BiVAD	120 mcg/kg	None, cerebral hypoperfusion?	POD 9 cerebral hypoperfusion, death
Kogan, et al.	Biomedicus Centrifugal Pump RVAD	35 mcg/kg x 2 doses	None	Recovery
Potapov, et al.	Berlin Heart AG BiVAD	120 mcg/kg, 60 mcg/kg	None	Chest closure & nml function of VAD
Reade, et al.	Abiomed BVS 5000 LVAD	35 mcg/kg	Extensive clot in the LVAD inflow chamber	Death
Saeed, et al.	HeartWare HVAD	90 mcg/kg	Thrombus in RA and SVC	Death
Tarzia, et al.	Berlin Heart AG BiVAD	120 mcg/kg	None	Nml function of VAD
Zietkiewicz, et al.	POLVAD LVAD	20 mcg/kg, 30 mcg/kg	None	Nml function of VAD, but death

Off-label use of recombinant activated factor VII in intractable haemorrhage after cardiovascular surgery: an observational study of practices in 23 French cardiac centres (2005–7)☆

Marie Hacquard [a,b,c,1,*], Marion Durand [a,b,d,1], Thomas Lecompte [a,b,c], Stéphanie Boini [e,f,b], Serge Briançon [e,f,b], Jean-Pierre Carteaux [a,b,d]

- 37 patient with MCS received rFVIIa
  - 29 ECMO, 7 transcutaneous VAD, 2 TAH
- Treatment in the OR for 18 pts
- Mean dose 65.3 mcg/kg (24-120 mcg/kg)
- Bleeding stopped in 10 pts, was reduced in 14 pts and was unchanged in 13 pts
  - Thrombotic rate was 27% (n=10)
  - Survival rate at 28 days = 45.7%

Eur J Cardiothoracic Surg. 2011;40:1320-1327.

High Incidence of Thromboembolic Events in Left Ventricular Assist Device Patients Treated With Recombinant Activated Factor VII

Brian A. Bruckner, MD,[a] Daniel J. DiBardino, MD,[a] Qian Ning, PA-C,[b] Alfred Adeboygeun, MD,[b] Karim Mahmoud, MD,[b] Jamie Valdes, MD,[b] John Eze, MD,[b] Paul M. Allison, MD,[b] Denton A. Cooley, MD,[b] Igor D. Gregoric, MD,[b] and Oscar H. Frazier, MD[b]

- Single center, retrospective review of 62 patients who received an LVAD and rFVIIa
- Stratified by low dose (10-20 mcg/kg, n = 32) vs high dose (30-70 mcg/kg, n = 30)
- Measured correction of coagulation abnormalities, transfusion requirements and thromboembolic events

J Heart Lung Transplant. 2009;28:785-790.

VAD's and rFVIIa – Efficacy

Table 3. Significant Group Differences in Transfusion Requirements

	Group	
	Low dose: 10–20 μg/kg (n = 32)	High dose: 30–70 μg/kg (n = 30)
Packed red blood cells (units)		
Before	24.5 ± 14.2 (3–85)	29.8 ± 35.6 (2–118)
After	10.2 ± 8.9 (1–32)	11.9 ± 12.9 (0–48)
p-value	0.002	0.003
Fresh-frozen plasma (units)		
Before	23.4 ± 21.3 (0–86)	28.4 ± 33.1 (3–115)
After	6.9 ± 7.5 (0–30)	10.6 ± 11.0 (0–44)
p-value	<0.0001	0.002
Platelets (units)		
Before	35.4 ± 24.1 (4–105)	29.5 ± 27.2 (0–95)
After	13.6 ± 19.7 (0–71)	8.8 ± 11.8 (0–40)
p-value	<0.0001	<0.0001

J Heart Lung Transplant. 2009;28:785-790.

VAD's and rFVIIa - Safety

Table 4. Summary of Thromboembolic Events

Complication	Group: Low dose: 10–20 μg/kg ($n = 32$)	Group: High dose: 30–70 μg/kg ($n = 30$)	Total ($n = 62$)
Stroke	0	2	2
Deep venous thrombosis	2	1	3
Myocardial infarction	0	1	1
Pulmonary embolism	1	2	3
Vascular occlusion	0	3	3
Ventricular clot	0	2	2
Total (%)	3 (9.4)	11 (36.7)	14 (22.6)

J Heart Lung Transplant. 2009;28:785-790.

GIB: subsequent thrombosis risk

- Stulak and collegues
- 2003-2011, 389 patients CF-LVAD, dual center
- Analyzed GI bleeding and thrombotic events
- 0.45 GI bleeds/patient-year of support
- 0.31 Thromb-embolic events/patient-year of support
- 7.4-fold increase in TE after a GIB!
  - 14.5-fold increase if > 70 years old
- Morbidity

J Heart Lung Transplant. 2014;33:60–64.

LVAD Thrombosis

- Device related thrombosis 0.2 events/patient-year
  - literature suggests increasing rates
- Risks factors and pathophysiology
  - Multifactorial

Pharmacotherapy. 2015;35(1):79-98

Device Thrombosis Pathophysiology

Table 1 Factors That May Increase Propensity to Pump Thrombus Formation in Continuous-Flow Pumps

Pump-related

1. Intrinsic heat generated by rotational movement of pump
2. Blood-contacting surface interactions
3. Shear stress-induced platelet activation
4. Regions of flow field stasis
5. Thrombus formation at cannulation site
6. Outflow graft impingement by outflow protector (now corrected)
7. Inflow cannula migration and malposition

Patient-related

1. Atrial fibrillation
2. Pre-existent atrial or ventricular thrombus
3. Presence of left sided mechanical prosthesis
4. Infection or sepsis
5. Non-compliance
6. Low flow due to:
   a. Cannula positional change over time (weight gain or loss, bending torso)
   b. Right-sided heart failure
   c. Hypovolemia
   d. Hypertension
7. Hypercoagulable state:
   a. Protein C deficiency
   b. Protein S deficiency
   c. Anti-thrombin deficiency
   d. Plasminogen deficiency
   e. Lupus anti-coagulant
   f. Heparin-induced thrombocytopenia
   g. Activated protein C deficiency
   h. Factor V Leiden
   i. Prothrombin G20210A mutation
   j. Malignancy

Management-related

1. Sub-therapeutic international normalized ratio
2. Absence of anti-platelet therapy
3. Inflow cannula malposition at implant
4. Infection management
5. Low flow due to:
   a. Low speed setting to manage gastrointestinal bleeding and/or aortic insufficiency
   b. Sub-optimal hypertension management

J Heart Lung Transplant. 2013;32:667–670.

Pharmacotherapy
HeartMate II®

- IIb/IIIa inhibitors (eptifibatide)
  - 0.1-2 mcg/kg/min (+/- bolus)
  - Up to 6 days in duration
  - Most with parenteral anticoagulant, therapeutic INR, anti-platelet therapy unknown
- Combined literature cohort
  - 27 patients
    - 7 success, 8 deaths, 13 bleeding complications
    - Limitations to currently available literature
- CAUTION

Pharmacotherapy. 2015;35(1):79-98

Pharmacotherapy
HeartMate II®

- Direct Thrombin inhibitors
  - Theoretical advantages/limitations
    - Greater efficacy in prevention of clot generation?
    - Inferior in attenuating clot propagation/strength?
  - No convincing literature to support use
    - Hirudin and argatroban in 5 case reports
      - Dose not reported
    - Bleeding complications
  - Included in thrombosis algorithm

J Heart Lung Transplant. 2013;32:667–670.
Pharmacotherapy. 2015;35(1):79-98.

Pharmacotherapy
HeartMate II®

- Fibrinolytics
  - Alteplase reported, dosage varies
  - Intraventricular (systemic) administration
  - 4 published case reports
    - Patient outcomes not reported in detail
  - CAUTION

Pharmacotherapy. 2015;35(1):79-98.

Pharmacotherapy
HeartWare HVAD®

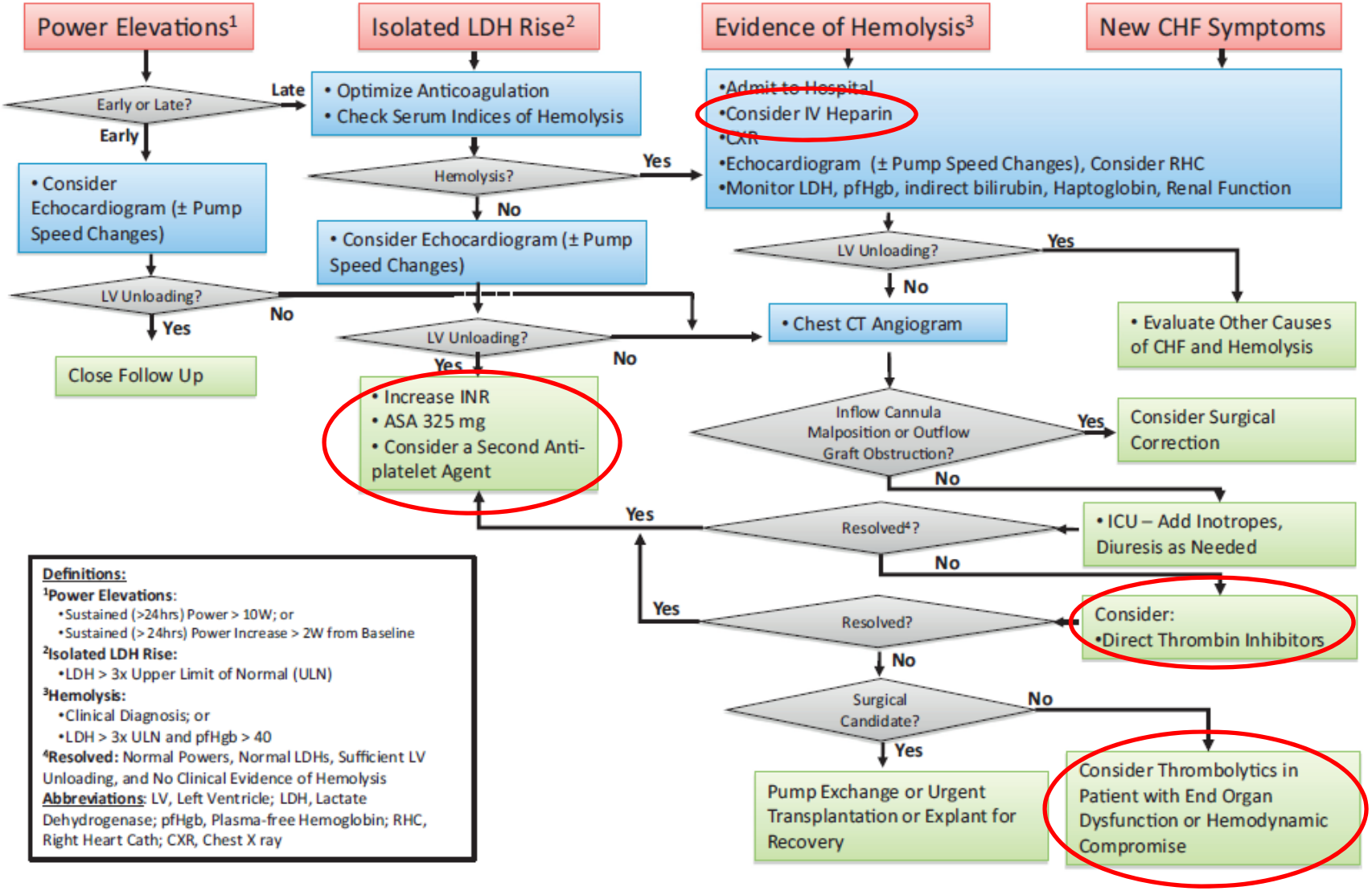
- IIb/IIIa inhibitors
  - Insufficient case reports
- Direct thrombin inhibitors
  - No data
- CAUTION

Pharmacotherapy. 2015;35(1):79-98.

Pharmacotherapy
HeartWare HVAD®

- Fibrinolytics
  - > 30 reported attempts (cases/BTT trials)
  - Frequent success, > 50%
  - Mostly alteplase
    - Total 15-60mg intraventricular/peripheral/unknown
    - 1 mg/min intraventricularly for 20-30 minutes
  - Strongest evidence, yet limitations
  - Caution
- **Aggressive medication therapy limits first line definitive therapy – Surgical Intervention**

Thrombosis Algorithm



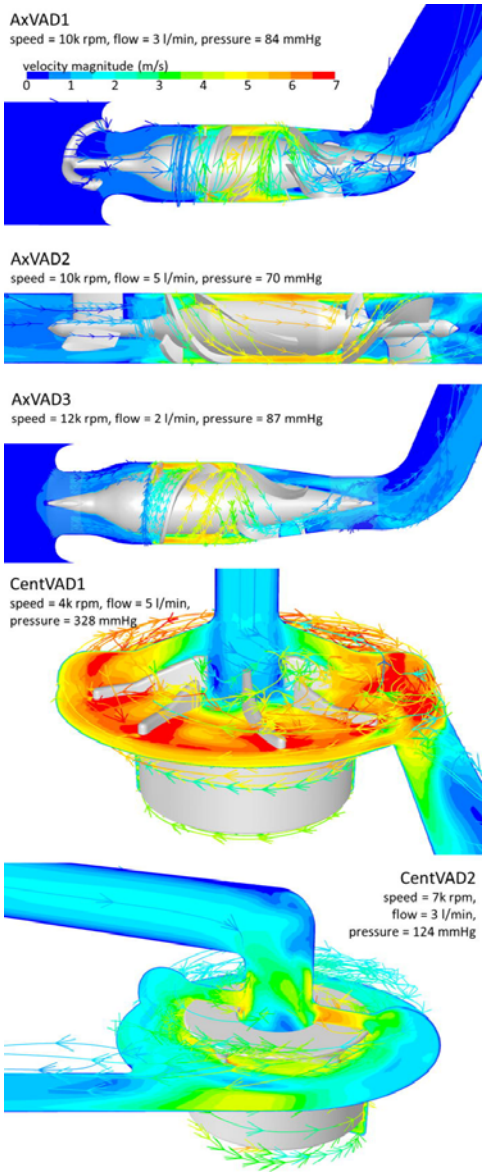
J Heart Lung Transplant. 2013;32:667–670.

Other strategies

- Thromboelastrography (TEG)
- Platelet aggregation studies
- Literature is limited but emerging
- Consider in consultation with expert multidisciplinary team
  - Blood center physician/transfusion medicine
  - Hematology
  - Advanced heart failure (VAD/transplant)
  - Pharmacist

Characteristics of LVAD thrombosis

- Heart failure symptoms
- Hematuria
- Hemolysis markers
  - LDH elevation/Plasma free Hgb
- LVAD not unloading
- Power “spikes”



Pharmacotherapy. 2015;35(1):79-98.

J Biomech Eng. 2012Aug;134(8):081002.

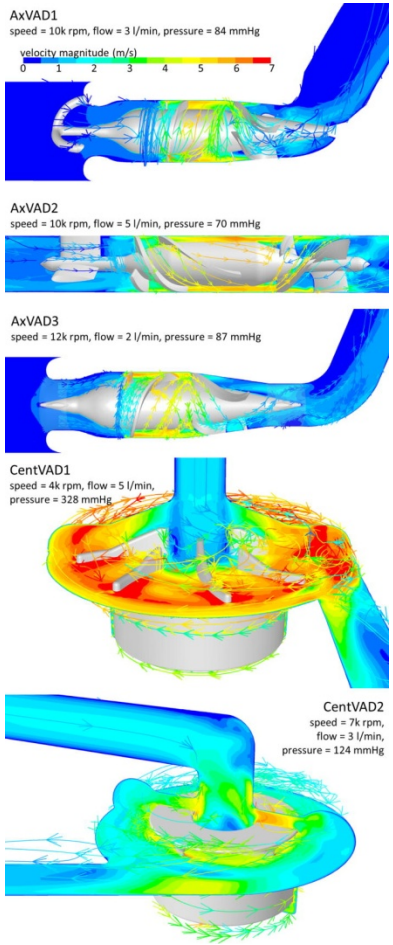
Pharmacologic options

- Suspected device thrombosis?
  - Optimize anti-thrombotic regimen per protocol
    - INR goal, anti-platelet therapy
    - Consider parenteral anticoagulation
      - Heparin infusion – protocols per institution protocol
      - Surgery is possible intervention
  - Other pharmacologic options?
  - Device considerations
    - Axial vs. centrifugal

J Heart Lung Transplant. 2013;32:667–670.

Other Strategies
Anemia in the LVAD recipient

- Hemolysis is a known LVAD complication
- Hemolysis contributes to anemia
- Any medications that allow Red Blood Cells tolerate LVAD turbulence?



Case Report - Pentoxifylline

- LVAD BTT patient with GI bleeding/anemia
- Anti-thrombotics reduced
- Anemia via hemolysis persists without evidence of bleeding
- Pentoxifylline added after transfusion
- At 60 days Hgb stable and LDH near normal

- Increases erythrocyte flexibility and reduces whole blood viscosity
- No platelet inhibition/bleeding risk
- Reduce mechanical hemolysis?

ASAIO Journal. **2013; 59:526–527.**

Anemia and LVAD

- Likely at least ½ LVAD patients anemic
- Some centers > 50% bridge-to-transplant
- Erythropoiesis stimulating agents (ESA's) may increase hemoglobin (Hgb) without transfusions
  - Transfusions = risk for sensitization
- ESA's may contribute to thrombotic risk
- Risk versus benefit justified?

J Am Coll Cardiol HF. 2015;3:146-53.
Pharmacotherapy. 2014 Jul;34(7):719-32.

ESA in LVAD review

- Nassif, et al. JACC 2015
- Retrospective, single-center review
- 221 patients HMII LVAD
- Receiving ESA vs. no ESA
- Primary outcome: Pump thrombosis (PT)
  - 180 days
  - Secondary: mortality, stroke

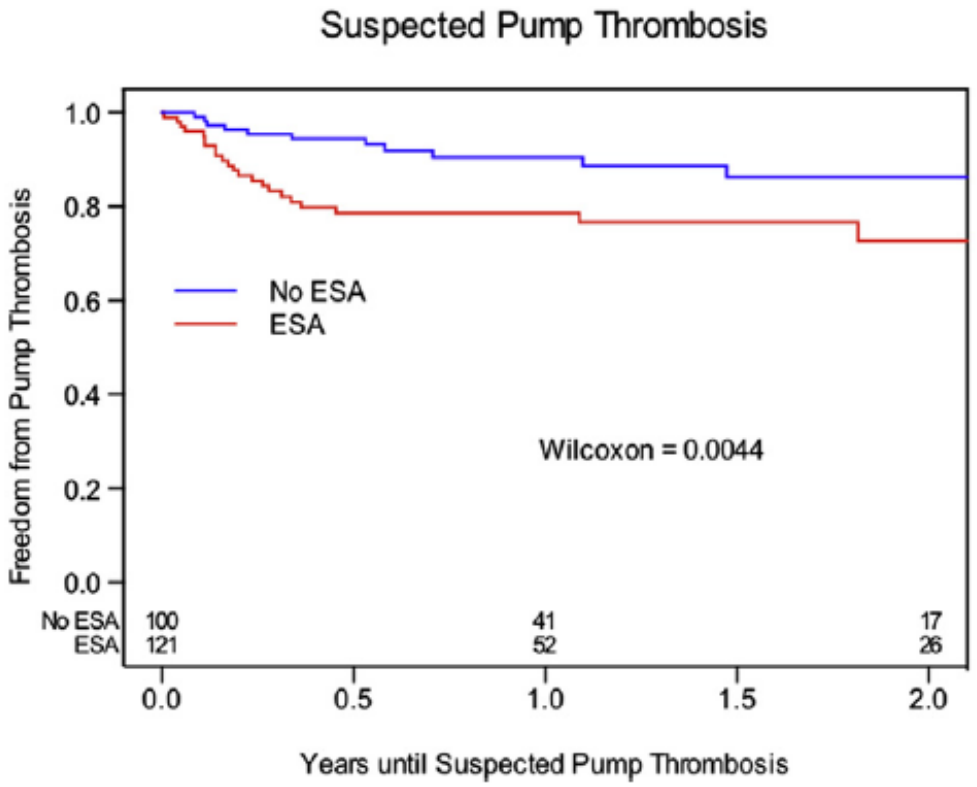
J Am Coll Cardiol HF. 2015;3:146-53.

Nassif, et al. JACC 2015

- PT: 37 patients
  - ESA 23%, no ESA 12%, p=0.03
  - HR=2.35, 95% CI 1.38-4, p=0.002
  - Dose related
    - Each 100 unit increase (darbopoetin) = 10% increase PT
    - HR=1.1, 95% CI 1.04-1.16; p<0.001
  - No difference in INR or Hgb at time of PT
  - No difference in admit/discharge CrCl, Hgb, INR

J Am Coll Cardiol HF. 2015;3:146-53.

FIGURE 1 Freedom From Suspected Pump Thrombosis



J Am Coll Cardiol HF. 2015;3:146-53.

Nassif, et al. JACC 2015

- Secondary outcomes
  - Inverse weighting of propensity scores used to reduce confounding by variables that may impact the administration of an ESA

J Am Coll Cardiol HF. 2015;3:146-53.

TABLE 2 Clinical Outcomes and Hazard Ratios Before and After Inverse Weighting for Patients Receiving LVAD Support With and Without Use of ESAs (n = 221)

	Before Inverse Weighting		After Inverse Weighting	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Suspected pump thrombosis	2.26 (1.15–4.40)	0.002	2.35 (1.38–4.00)	0.002
All-cause mortality	1.56 (0.93–2.62)	0.09	1.62 (1.12–2.33)	0.01
Stroke	0.59 (0.26–1.31)	0.19	0.55 (0.30–1.02)	0.06
Ischemic stroke	0.59 (0.20–1.74)	0.34	0.51 (0.21–1.24)	0.14

J Am Coll Cardiol HF. 2015;3:146-53.

ESA and the LVAD patient

- Study has limitations
- Extends cautious use of ESA to the heart failure patient with an LVAD
- Another factor to add to the Bleeding versus Clotting dilemma in the LVAD recipient