Long-Term Outcomes After Successful Treatment of TTP

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Historical Perspective

- Prior to PEX therapy nearly uniformly fatal
- Rock et al in 1991
  - PEX superior to plasma infusion
    - Mortality 10-20%
- Increasing numbers of survivors
  - Able to now evaluate for long-term issues

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What Took So Long?

- Continuity of care
  - Referral back to local hematologist
  - Not followed
    - Normal platelet count, normal patient
- Longitudinal follow-up of patients
  - Emphasis of research programs
- TTP patient group meetings
  - University of Oklahoma

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Neurocognitive Deficits and TTP
Oklahoma TTP-HUS Registry

- 24 patients with previous history of TTP
  - ADAMTS13 <10% at presentation
  - Normal physical exam
  - Normal MMSE
    - Screening for dementia

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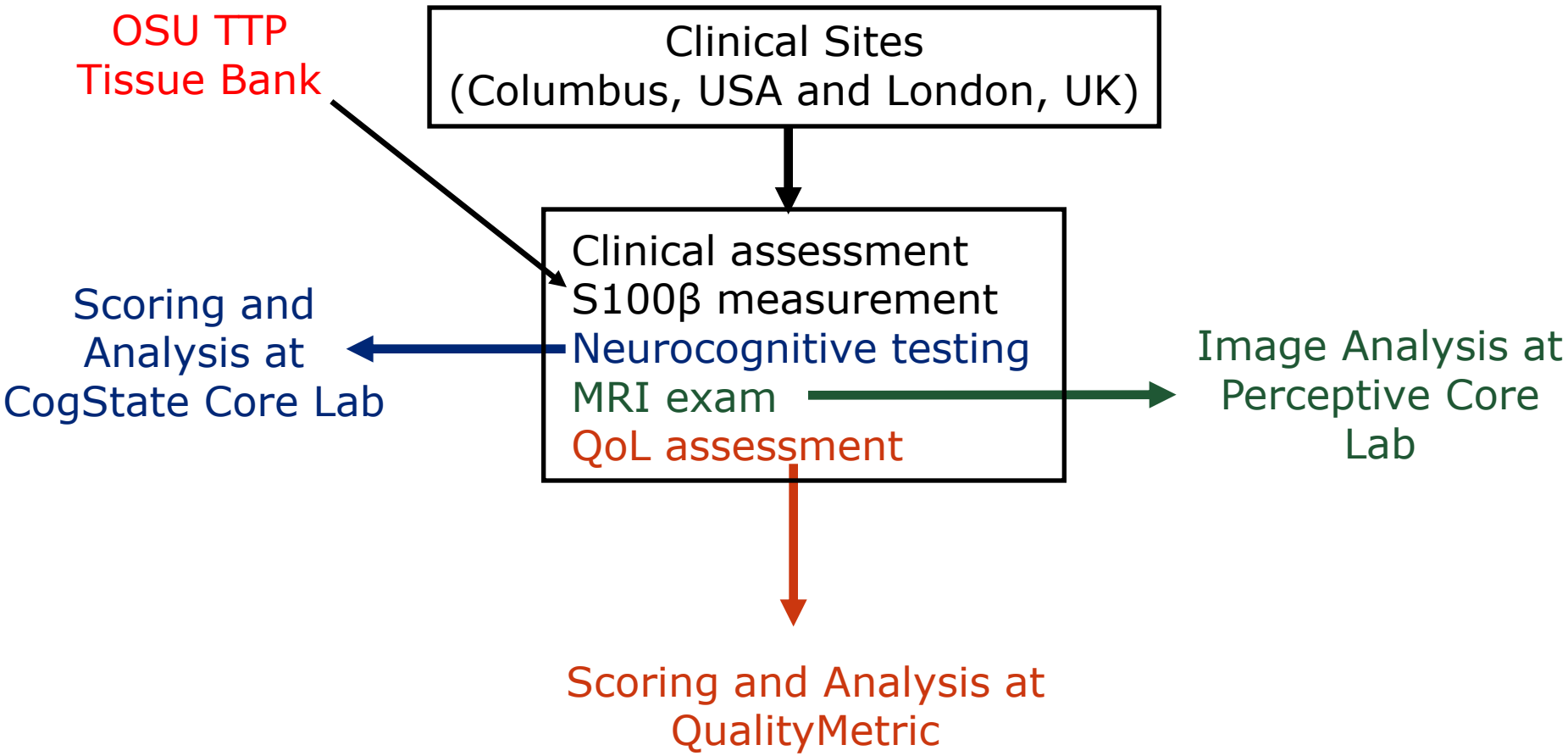
Kennedy et al. *Transfusion*, June 2009

Neurocognitive Deficits and TTP
Oklahoma TTP-HUS Registry

- Significantly worse as a group on 4/11 cognitive domains tested
  - Complex attention/concentration skills
  - Information processing speed
  - Rapid language generation
  - Rote memorization
    - 21/24 (88%) below expectations on at least 1/11 domains tested
- Not predictive: age, features of TTP, multiple episodes, interval from last episode

Kennedy et al. *Transfusion*, June 2009

Data Collection Scheme



Neurocognitive Function Testing

CogState® Neurocognitive Test Battery

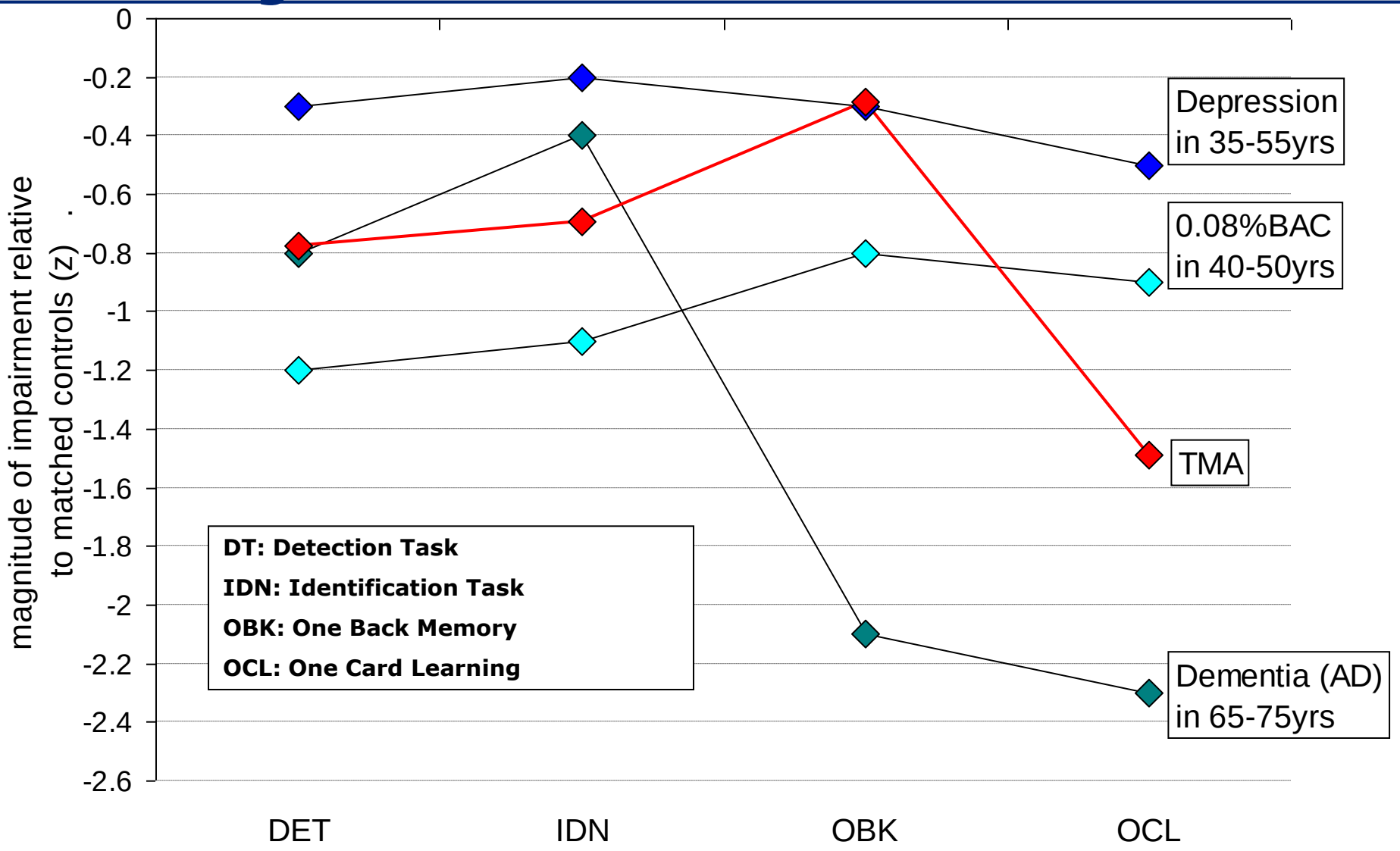
- Computerized, self-administered, rapid testing system
- Large reference dataset from normal population
- Established validity and utility for detection of disease- and drug-related neurocognitive impairment

- Detection Task – psychomotor function / speed
- Identification – attention / vigilance
- One Card Learning – visual learning & memory
- One Back Memory – working memory
- Groton Maze Learning Test – executive function

Prevalence of Neurocognitive Deficits

- 31% (9/29) unable to complete test of executive function (GMLT), no score imputed
- 62% (18/29) patients <1 SD below age-matched norm on at least 1 of the 4 other tests
- 52% (15/29) scored <2 SD below age-matched norm on at least 1 of the 4 other tests
- 45% (13/29) patients <1 SD below age-matched norm on at least 2 of the 4 other tests

Comparison of Neurocognitive Deficits in Differing Disease States



Correlations Among Measures Of CNS Injury

Neurocognitive (NC) deficits and MRI evidence of structural damage:

- 15/29 patients with NC impairment
  - 7 of these 15 also have abnormal MRI
- 9/23 patients with abnormal MRI
  - 7 of these 9 also have NC impairment
- NC testing may be more sensitive than MRI for detection of CNS injury in TMA

bjh correspondence

Long-term, sub-clinical cardiac and renal complications in patients with multiple relapses of thrombotic thrombocytopenic purpura

- At presentation
  - 17/22 (77%) with proteinuria
  - 15/22 (68%) had increased serum creatinine
- During follow-up (median 5 years)
  - Normal renal function
  - No cardiac findings
  - 2 patients with newly diagnosed HTN

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Viswanathan et al. BJH, 2010

Chronic End-Organ Complications

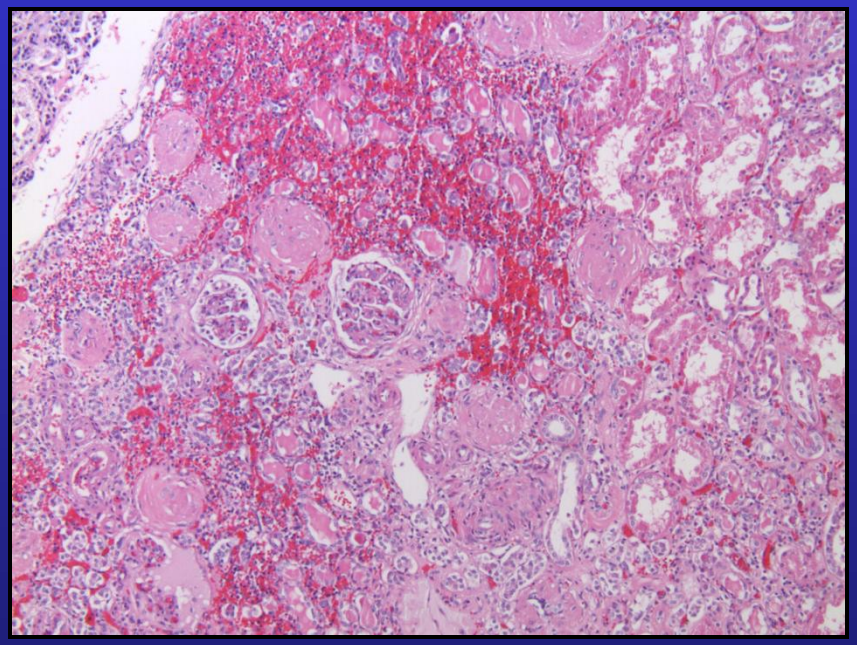


Figure 1. Sclerotic glomeruli and atrophic tubules with petechial hemorrhage

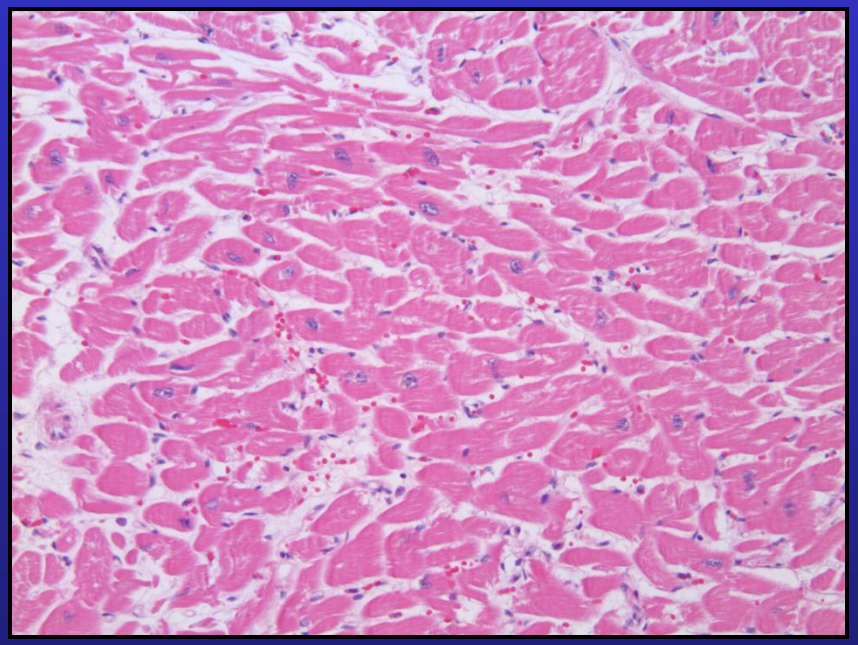


Figure 2. Hypertrophic myocytes

Viswanathan et al, Br J Haematol. 2010 May;149(4):623-5.

Mortality and Morbidities during Long-Term Follow-Up after Recovery from Thrombotic Thrombocytopenic Purpura (TTP)

Jessica A. Reese, Zayd L. Al-Nouri, Cassandra C. Deford, Lauren M. Stewart, Deirdra R. Terrell, Sara K. Vesely, Johanna A. Kremer Hovinga, Bernhard Lämmle, James N. George

Objective

- **To document the long-term outcomes of patients following recovery from TTP associated with acquired severe ADAMTS13 deficiency (<10%)**

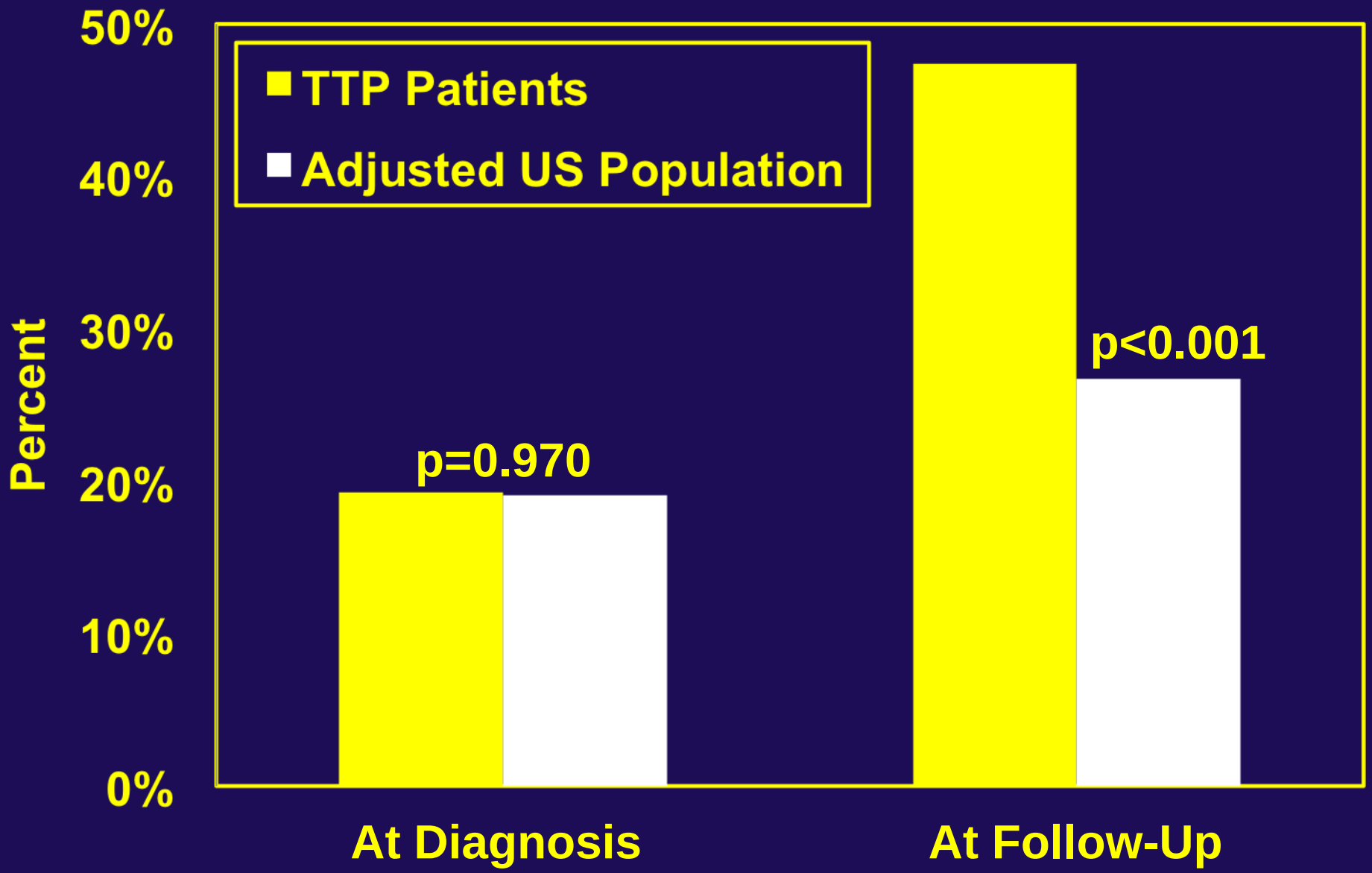
Methods: Follow-Up

- Telephone contact, 1-2 times per year
- Support group meetings, 3 times per year
- Clinic evaluation, once per year

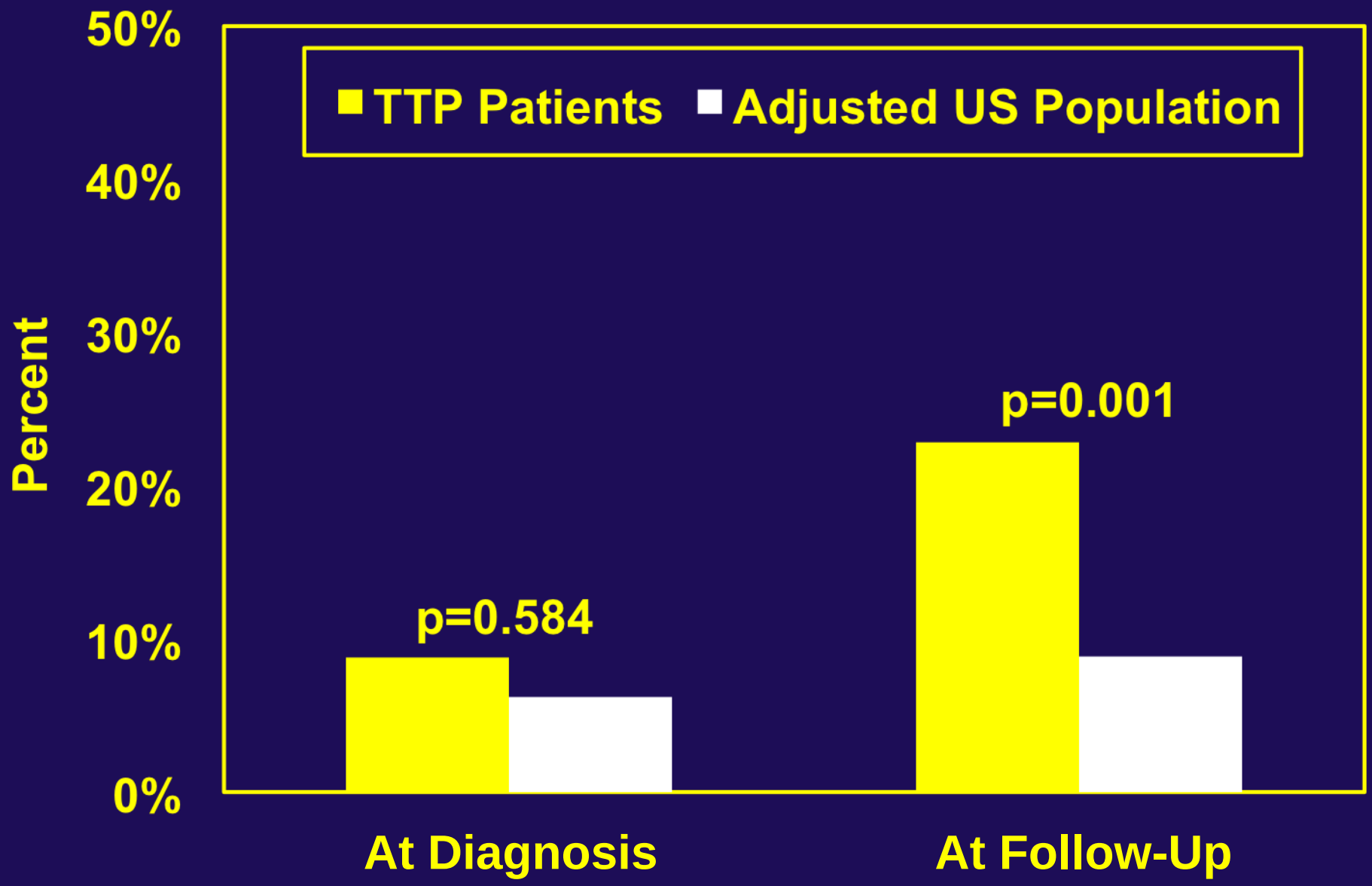
Results

- 57 survived their initial episode:
  - median age was 39 years (range 9-71)
  - 45 (79%) were women
  - 21 (37%) were black

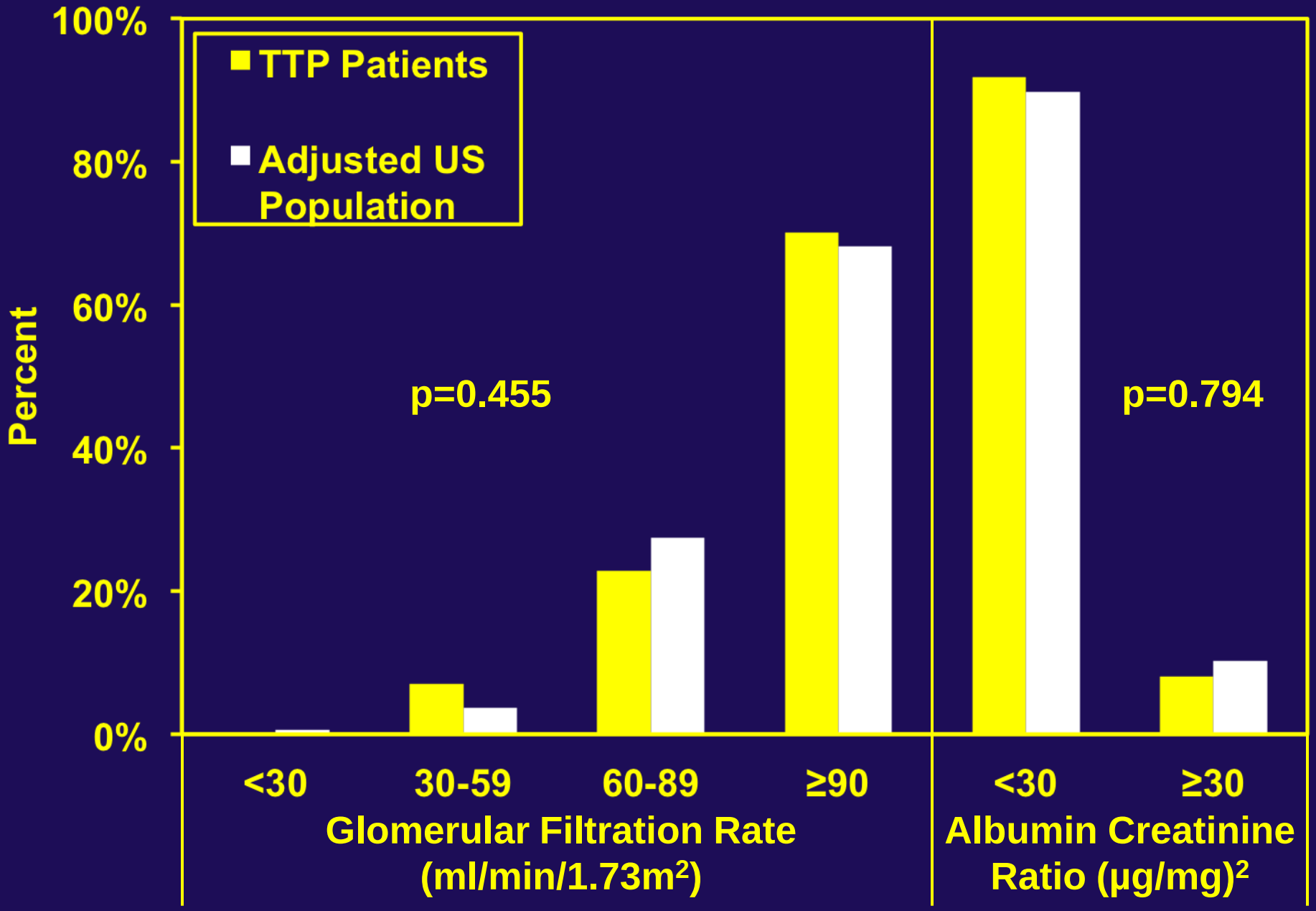
Hypertension



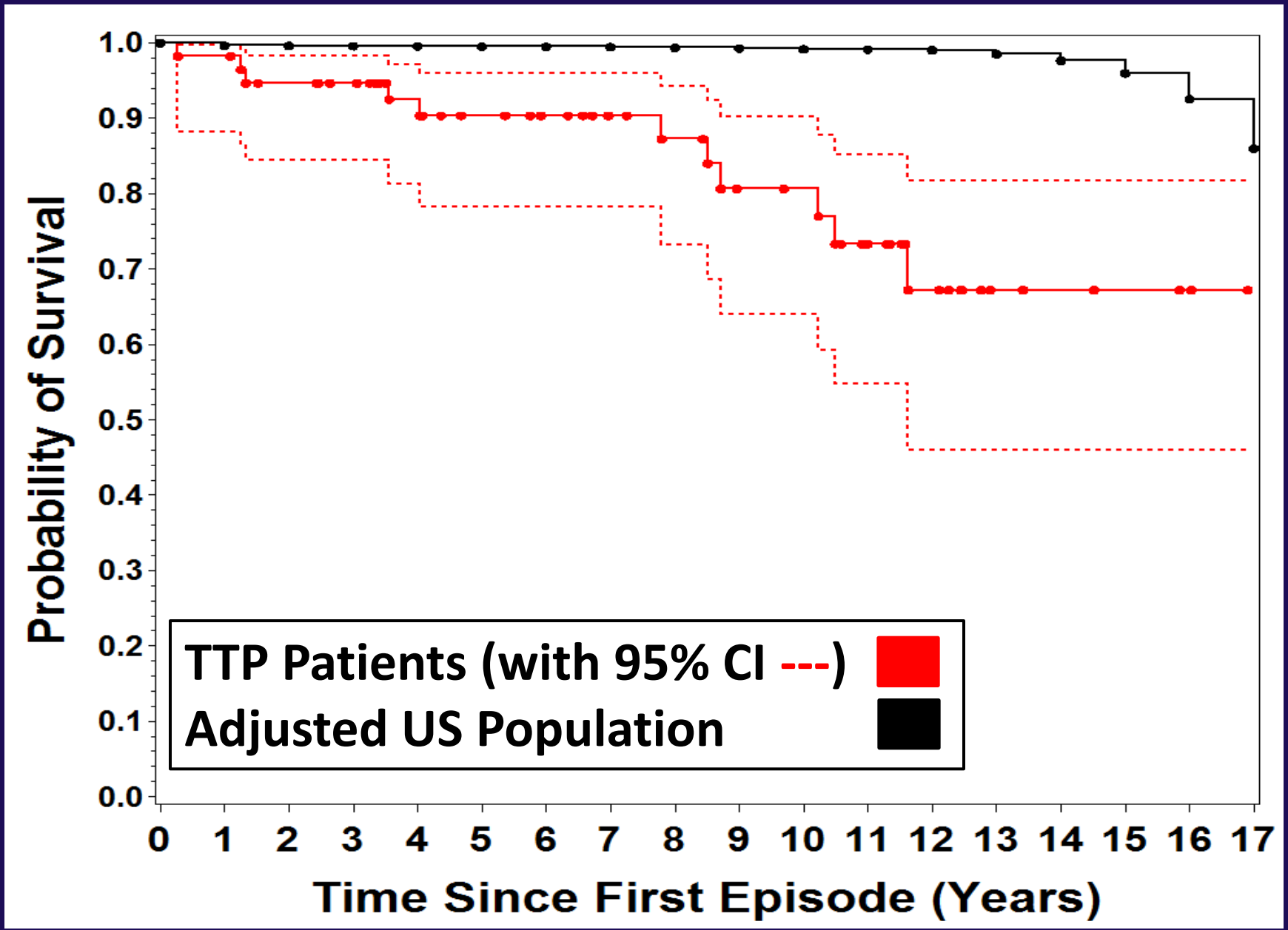
Diabetes


50%
40%
30%
20%
10%
0%
Percent
TTP Patients
Adjusted US Population
p=0.584
p=0.001
At Diagnosis
At Follow-Up

Kidney Function



Probability of Survival



Probability of Survival

Year(s) after initial episode	TTP Patients (95% CI)	Adjusted US Population
1	0.98 (0.87, 0.99)	0.997
5	0.90 (0.78, 0.96)	0.995
10	0.77 (0.59, 0.88)	0.992
15	0.67 (0.46, 0.82)	0.958

Attributed Causes of Death

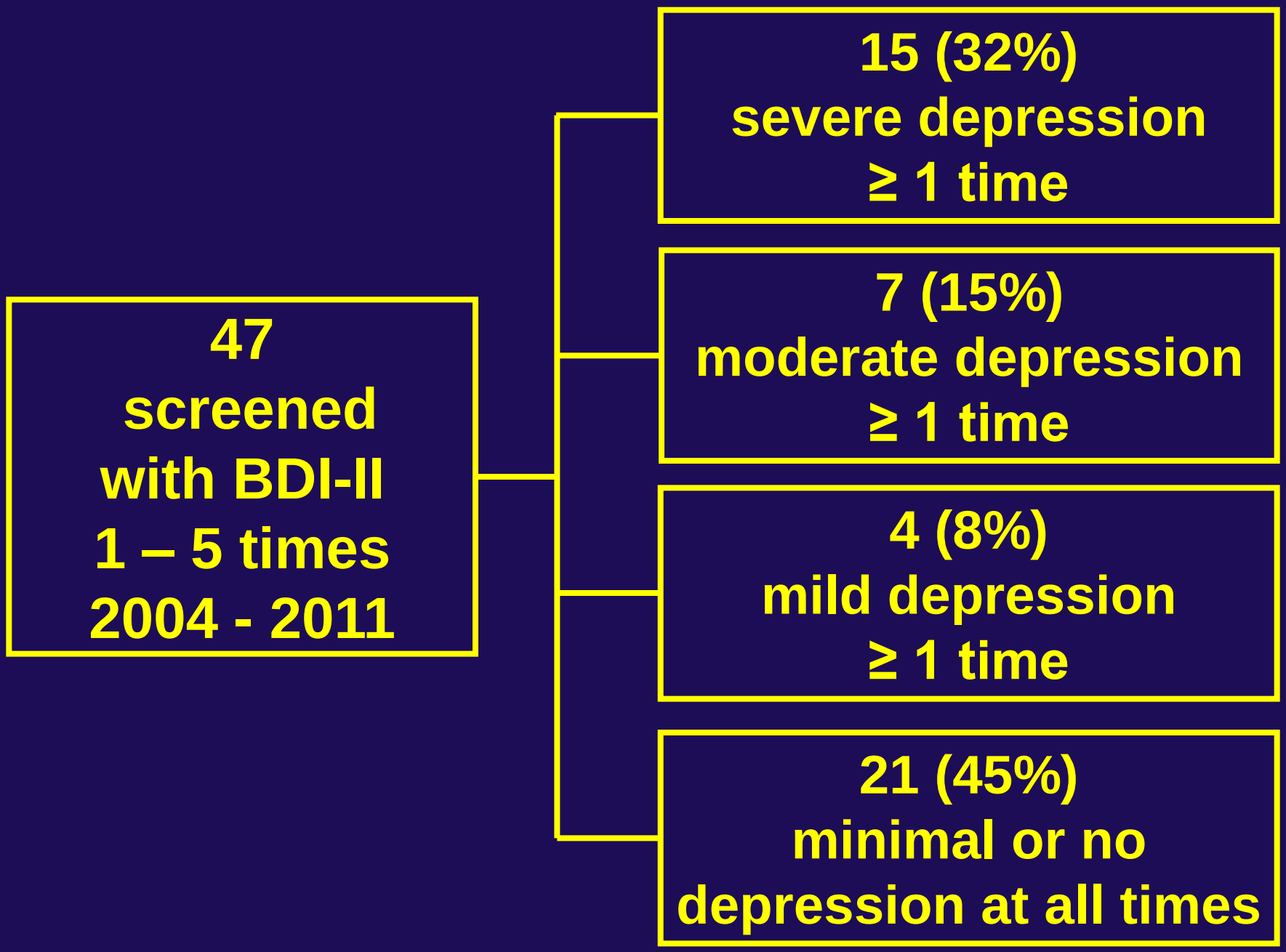
- 1 – TTP relapse, confirmed by autopsy
- 1 – MI following recovery from TTP relapse; no TTP at autopsy
- 9 – Deaths with no evidence of TTP relapse
  - cardiovascular disease (4), ovarian cancer (1), sepsis (1), stroke (1), liver cirrhosis (1), intestinal hemorrhage (1)

Major Depression during Long-Term Follow-Up after Recovery from Thrombotic Thrombocytopenic Purpura (TTP)

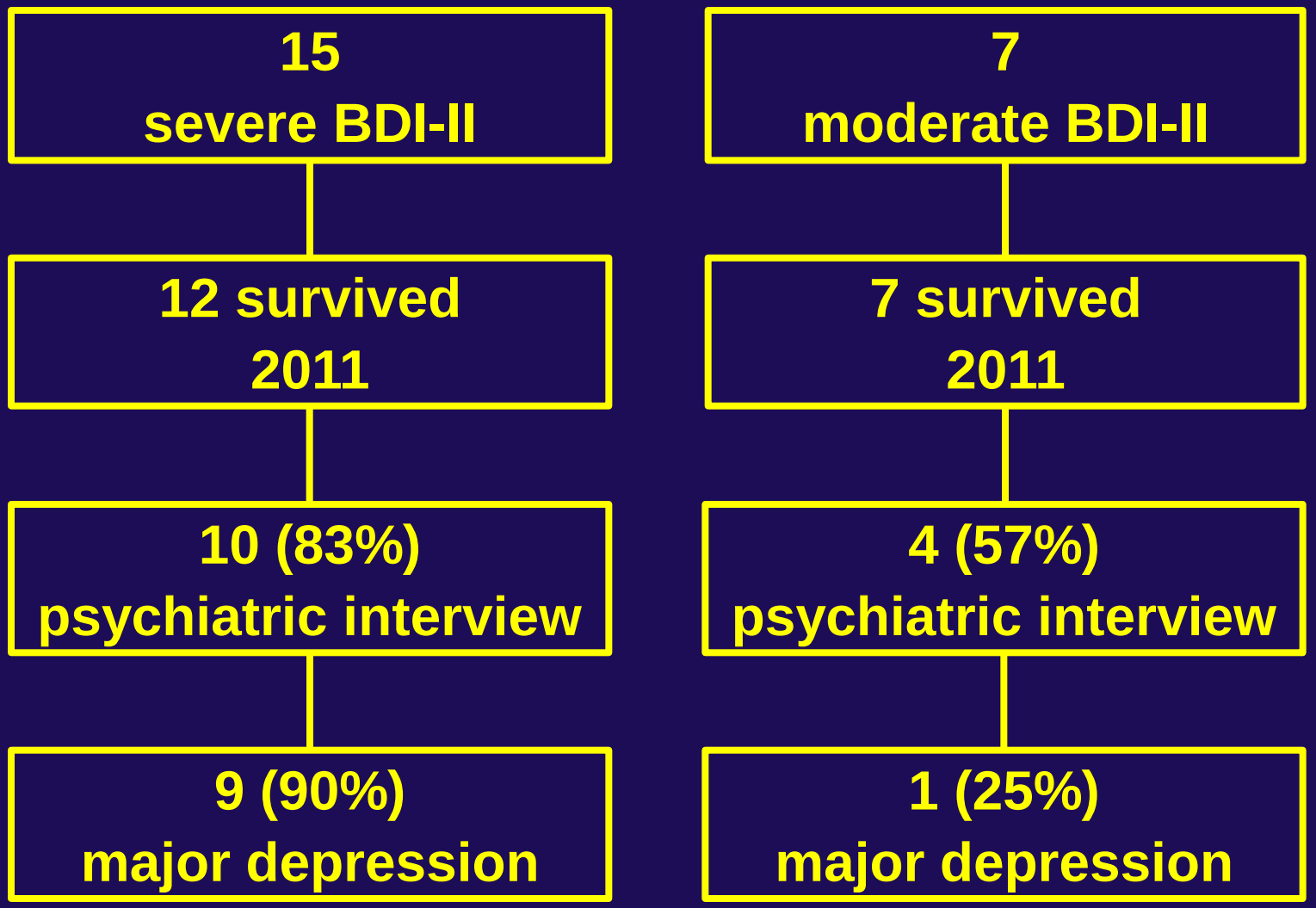
Cassandra C. Deford, Lauren H. Schwartz, Jedidiah J. Perdue, Jessica A. Reese, Johanna A. Kremer Hovinga, Bernhard Lämmle, Lauren M. Stewart, Zayd L. Al-Nouri, Deirdra R. Terrell, James N. George, Sara K. Vesely

Methods: Depression Measures

- Beck Depression Inventory-II (BDI-II) (2004-2011)
  - 21 question screening measure for depression within previous 2 weeks
- In-person structured psychiatric interview (2011)
  - Definitive method for diagnosis of major depressive disorder (major depression)


47
screened
with BDI-II
1 – 5 times
2004 - 2011
15 (32%)
severe depression
≥ 1 time
7 (15%)
moderate depression
≥ 1 time
4 (8%)
mild depression
≥ 1 time
21 (45%)
minimal or no
depression at all times

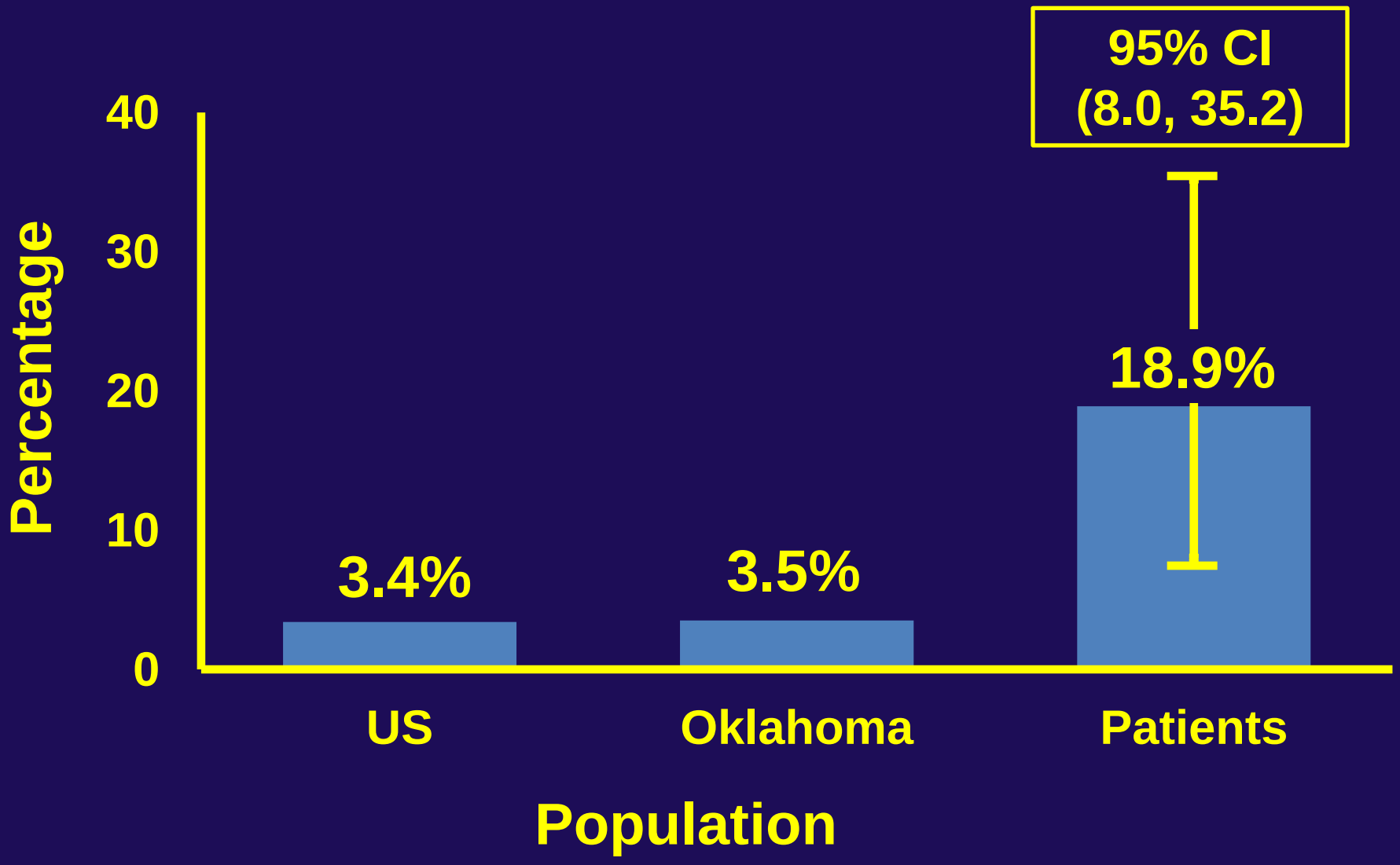
Psychiatric Interviews: 2011



Methods: Depression Measures

- Patient Health Questionnaire-8 (PHQ-8) (2012)
  - 8 question screening measure for depression within the previous 2 weeks
  - Used by the Behavioral Risk Factor Surveillance System (BRFSS)
  - Patients were screened 6.32 years (range, 1.79-16.12 years) after their initial episode of TTP

Major Depression: PHQ-8



Conclusions

- The prevalence of major depression is significantly increased in patients during long-term follow-up after recovery from TTP
- Recognition and appropriate management of major depression are critical components of the care of these patients

The Oklahoma TTP-HUS Registry
Risk of Recurrence with a Subsequent Pregnancy

Oklahoma Registry:

- **20 women with 35 subsequent pregnancies**

Systematic review of all published case reports:

- **44 articles described 49 women with 70 subsequent pregnancies**

***Transfusion* 2004; 44:1149**
(+ subsequent experience)

Recurrent TTP with a Subsequent Pregnancy

Category	Oklahoma	Literature
Congenital	-	12/13 (92%)
Acquired		
idiopathic	3/11 (27%)	11/18 (61%)
pregnancy	2/22 (9%)	18/39 (46%)
bloody diarrhea	0/2	-

Transfusion 2004; 44:1149

Pregnancy and Relapse Risk of TTP

- 5 patients with a previous history of TTP
  - 3/5 pregnancy-related (cases 1,2,and 4)
  - 1/5 multiple previous episodes (case 3)
  - 4 required PEX based upon pretreatment ADAMTS13 activity <5%

Table 3 ADAMTS 13 activity levels (%) throughout pregnancy for cases 1–5 by Collagen Binding Assay (NR:66–126%) or *multimeric assay (NR:80–120%)

	Pre-pregnancy	10–16 weeks	20–26 weeks	Pre-delivery	6 weeks post partum
Case1	<5*	ND	ND	49*	ND
Case2	<5	5	16	30	<5
Case3	<5	<5	66	78	85
Case4	NA	<5	47	41	7
Case5	89*	90*	78*	93*	91*

Samples undertaken pre-exchange in cases 1–4 undergoing regular PEX. ND: not done. NA: not applicable.

Scully M et al. Blood, Coagulation and Fibrinolysis, 2006

bjh correspondence

ADAMTS13 activity and the risk of thrombotic thrombocytopenic purpura relapse in pregnancy

Patient	Circumstances	Week of gestation	ADAMTS13 activity (%)	Inhibitor level (BU)	Previous history of TTP
1	Pregnancy-related	22	<2·5%	1·5	No
2	Idiopathic	NA	<2·5%	57·6	No
3	Idiopathic	NA	<2·5%	5·2	No

Table II. ADAMTS 13 activity (inhibitor level in Bethesda units) in five pregnancies.

Patient	Pregnancy	Pre-pregnancy (1–11 months)	12–20 weeks	20 weeks- labour	Postpartum (4–6 weeks)	TTP/week of gestation
1	1	ND	ND	<2·5% (1·5)	<2·5% (3·2)	Yes/22
1	2	<2·5% (0·5)	<2·5% (0·7)	<2·5% (19·2)	<2·5% (0·5)	Yes/21
1	3	15·3% (0·5)*	14·8% (0·5)*	26% (0·5)*	<2·5% (2)	No/NA
2	1	<2·5% (22·4)	<2·5% (6·4)	<2·5% (2)	NA†	Yes/37
3	1	61·2% (0·5)	100% (0·5)	91·7% (0·5)	ND	No/NA

Raman R et al. *BJH,* 2011

Conclusions

- Significant increase in our knowledge of the long-term complications from a previous diagnosis of TTP
  - Greater number survivors
  - Patient support group
- Neurocognitive, vascular, and psychiatric complications are more common than recognized previously
- Increased awareness may lead to efforts to decrease the morbidity and mortality related to these chronic complications

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