HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

An Overview of Clinical Trials for PE: Will Any of Them Move The Needle?

Rachel P. Rosovsky, MD, MPH
Director, Thrombosis Research, Dept of Hematology, Mass General Hospital
Associate Professor of Medicine, Harvard Medical School
Immediate Past President, The PERT Consortium ™

@RosovskyRachel
HARVARD MEDICAL SCHOOL
Massachusetts General Hospital
Founding Members: Mass General Brigham

Yes, I believe they will

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Disclosures

Rachel P. Rosovsky, MD, MPH

- Institutional Research Support:
  - BMS, Janssen
- Advisory/Consultant:
  - Abbott, BMS, Boston Scientific, Dova, Inari, Inquis, Janssen, Penumbra
- National Lead Investigator, *Storm-PE,* Penumbra
- Immediate Past President, The PERT Consortium™

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Case

- 48 year old male presents to local hospital with acute SOB.
- CTA showed extensive bilateral PE and RV/LV ratio >1.
- Given one dose enoxaparin and sent to MGH.
- At MGH:
  - Vitals: 87% on room air (require 15 L NC oxygen), HR 150, RR 28, BP 140/79.
  - ECHO: RV dilated, hypokinetic, RVSP 54 mm Hg
  - Elevated troponin and BNP

RV = right ventricle
LV = left ventricle
NC = nasal cannula
MGH = Massachusetts General Hospital

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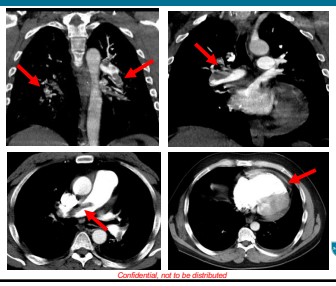
Bilateral PE and Right Heart Strain



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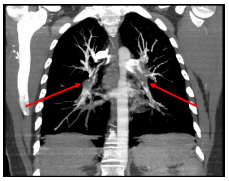
Pulmonary Embolism: Why do we worry?



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Pulmona matter?

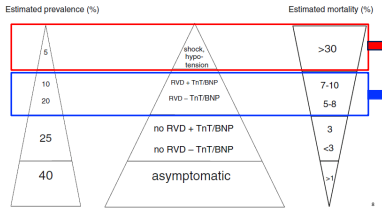
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

274 Death/Day → 12 Death/Hour → 1 Death/5 mins

Bedenar, Am J Prev Med 2010
Wendelboe et al. Thromb Haemost. 2020
Grosse et al. Thrombosis Research. 2016

VTE: venous thromboembolism

Most Patients with PE do Well … But Some Do Not



Becattini C, Agnelli G. Thromb Haemost. 2008
Abrahams van Doorn P, and Hartmann LC. Imaging Insights. 2011
Dalen JE. Chest. 2009;135

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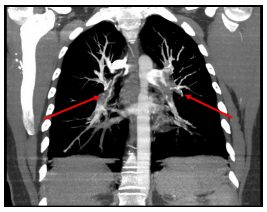
Pulmonary Embolism: Current Treatment Options



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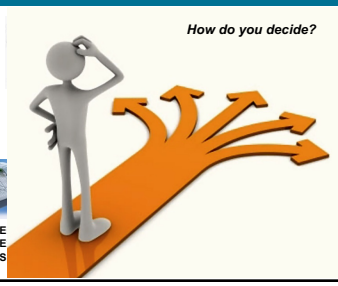
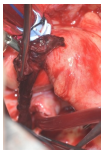
Lots of Options

Anticoagulation

Catheter Directed Thrombolysis



Pulmonary Embolectomy



Anticoagulation Saves Lives

ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM
A CONTROLLED TRIAL

TABLE II—RESULTS IN FIRST 35 CASES

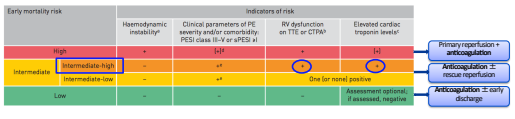
Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	16	0	0	1

TABLE III—RESULTS IN COMPLETE SERIES OF 73 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	54	0	1	2

Barritt. Lancet. 1960

Risk Stratification for Acute PE



Where does our patient fit in?

European Heart Journal 2019

Guidance in the Literature for Treatment of Massive/Submassive PE: Very Little

ESC European Society of Cardiology

European Heart Journal (2019) 00, 1–61
doi:10.1093/eurheartj/ehz405

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)

The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)

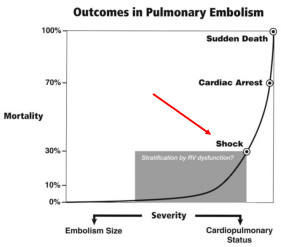
European Heart Journal 2019

Intermediate Risk Pulmonary Embolism

Reperfusion treatment		
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment.[282]	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy[e] or percutaneous catheter-directed treatment[e] should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE.[c,f 179]	III	B

14 European Heart Jo...

When does patient need advanced therapy?



Wood. Critical Care Clinics. 2011

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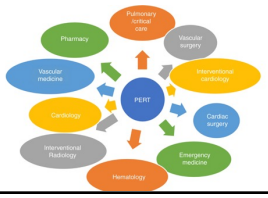
Case Decision-Making

- Intermediate High-risk PE
- Reassuring head imaging
- Expeditiously started on LMWH
- PERT called



- Do we have the data to support Catheter Directed Therapies for intermediate risk PE?

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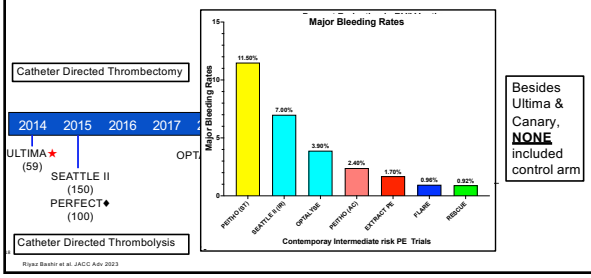
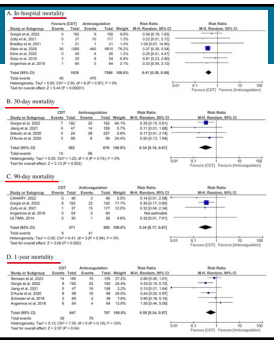
Catheter Directed Therapies



Besides Ultima & Canary, **NONE** included control arm

Riyaz Bashir et al. JACC Adv 2023

- 10,549 patients
- 15 studies
  - 2 RCTs
  - 12 observational



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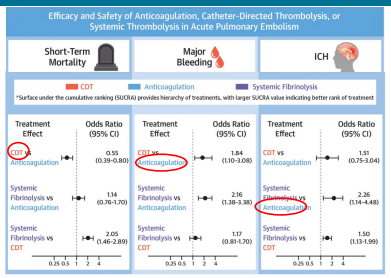
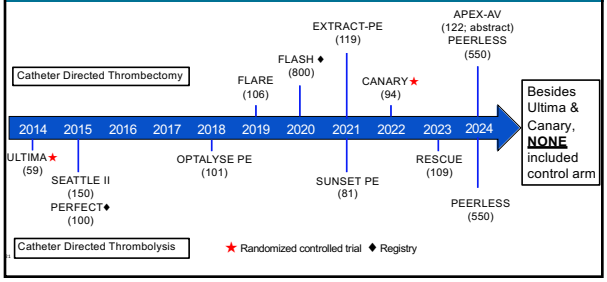
- >80,000 patients
- 45 studies
  - 17 RCTs
  - 2 prospective nonrandomized,
  - 26 retrospective observational.



Catheter Directed Therapies: Published Trials

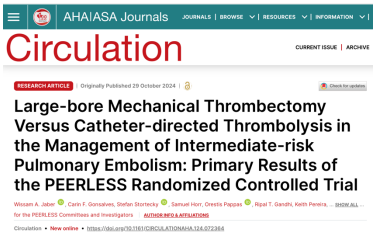


PEERLESS

LBMT vs CDT

↓ clinical deterioration and/or bailout and postprocedural ICU utilization

↔ no difference in mortality or bleeding.


AHAIASA Journals

Circulation

RESEARCH ARTICLE

Large-bore Mechanical Thrombectomy Versus Catheter-directed Thrombolysis in the Management of Intermediate-risk Pulmonary Embolism: Primary Results of the PEERLESS Randomized Controlled Trial

APEX-AV

- 122 patients
- Mean ↓ in RV/LV ratio from baseline to 48 hours post-procedure of **0.45**
- MAEs rate of 4.1%
- 35.5% mean ↓ in clot burden from baseline to 48 hours post-procedure

MAE: Major Adverse Event

Currently…

- Five **on-label** endovascular devices for acute pulmonary embolism
  - EKOS Ultrasound accelerated thrombolysis (USAT)
  - FLOWTRIEVER retrieval/aspiration system (LBAT)
  - INDIGO aspiration system (CAVT)
  - BASHIR pharmacomechanical thrombolysis (PMT)
  - ALPHA-VAC aspiration system

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- Do we have the data to support use of advanced therapy over anticoagulation for intermediate risk PE?
  - *Currently, we do **NOT have Level 1 evidence***
  - *Equipoise*
- Rationale for randomized controlled trials

Currently: Six Enrolling Prospective Randomized Trials

HI-PEITHO	PE-TRACT	STORM-PE TRIAL	PERFUSE	PEITHO-3	PERSEVERE	PEERLESS
RCT 1:1 EKOS VS. ANTICOAG INTERMEDIATE HIGH	RCT 1:1 ENDOVASC VS ANTICOAG INTERMEDIATE	RCT 1:1 INDIGO VS ANTICOAG INTERMEDIATE HIGH	RCT 1:1 FLOWTRIEVER VS ANTICOAG INTERMEDIATE	RCT 1:1 OF REDUCED DOSE ALTEPLASE VS UFH INTERMEDIATE HIGH	RCT 1:1 of FLOWTRIEVER VS SOC FOR HIGH RISK	RCT 1:1 FLOWTRIEVER VS CDT INTERMEDIATE HIGH
406 SUBJECTS 65 GLOBAL SITES	500 SUBJECTS 30 NORTH AMERICAN SITES	100 SUBJECTS 25 GLOBAL SITES	1200 PATIENTS	650 SUBJECTS	200 SUBJECTS	550 SUBJECTS 30 SITES
(PE)-RELATED MORTALITY, CARDIORESPIRATORY DECOMPENSATION OR COLLAPSE, NONFATAL SYMPTOMATIC AND OBJECTIVELY CONFIRMED RECURRENCE OF PE	PVO2 AT 90 DAYS NYHA CLASSIFICATION AT ONE YEAR ISTH MAJOR BLEED AT 7 DAYS	RV/LV RATIO AT 48 HOURS (PE)-RELATED MORTALITY, CARDIORESPIRATORY DECOMPENSATION OR COLLAPSE, NONFATAL SYMPTOMATIC AND OBJECTIVELY CONFIRMED RECURRENCE OF PE	ALL-CAUSE MORTALITY BY 30 DAYS CLINICAL DETERIORATION AND/OR BAILOUT BY 30 DAYS ALL-CAUSE HOSPITAL READMISSION BY 30 DAYS DYSPNEA SCORE AT 48-HOUR VISIT	ALL CAUSE MORTALITY, CLINICAL DETERIORATION, OR RECURRENT PE AT 30 DAYS	ALL-CAUSE MORTALITY CARDIAC ARREST WITH LOSS OF CONSCIOUSNESS REQUIRING CPR BAILOUT TO ALTERNATIVE THERAPEUTIC STRATEGY MAJOR BLEEDING** PERSISTENT NEED FOR ECMO	MORTALITY ICH ISTH MAJOR BLEEDING CLINICAL DETERIORATION ICU LOS. (DISCHARGE)
12 MONTHS	12 MONTHS	90 DAY FOLLOW UP	90 DAY FOLLOW UP	24 MONTH FOLLOW UP	90 DAY FOLLOW UP	30 DAY FOLLOW UP

Clinical Trials

- Medical Therapy
- Catheter Directed Thrombolysis
- Catheter Directed Thrombectomy

Medical Therapy: PEITHO-3

- Intervention
  - RCT 1:1 of reduced dose alteplase (0.6 mg/kg) vs UFH in intermediate high-risk PE
- Primary Outcome:
  - Clinical composite of death from any cause or hemodynamic decompensation or objectively confirmed recurrent PE within 30 days of randomization
- Study Enrollment
  - 250
- 24 month follow up

UFH = unfractionated heparin

Clinical Trials

- Medical Therapy
- Catheter Directed Thrombolysis
- Catheter Directed Thrombectomy

Catheter Directed Thrombolysis: HI-PEITHO

HI-PEITHO

EKOS™ (USCDT) + anticoagulation vs anticoagulation alone

The Higher-risk Pulmonary Embolism Thrombolysis Study

Principal Investigators/ Sponsor	Stavros Konstantinides, MD Kenneth Rosenfield, MD • PERT Consortium • University Mainz/PEITHO Network • Boston Scientific Corporation
Study Design	Randomized, controlled, open label, multicenter (up to 65 sites in US and Europe) **USCDT + anticoagulation vs anticoagulation alone** — **12 months**
Patients	**Enrollment of 406-544 patients,** adaptive based on planned interim analysis Eligibility criteria select **intermediate-high risk PE**
Primary Endpoint	**7-day** composite of: • **PE-related mortality** • **Cardiorespiratory decompensation or collapse** • **PE recurrence** (nonfatal symptomatic and objectively confirmed) Independent, blinded outcome adjudication

PE, pulmonary embolism; USCDT, ultrasound-assisted catheter-directed thrombolysis.

Clinical Trials

- Medical Therapy
- Catheter Directed Thrombolysis
- Catheter Directed Thrombectomy

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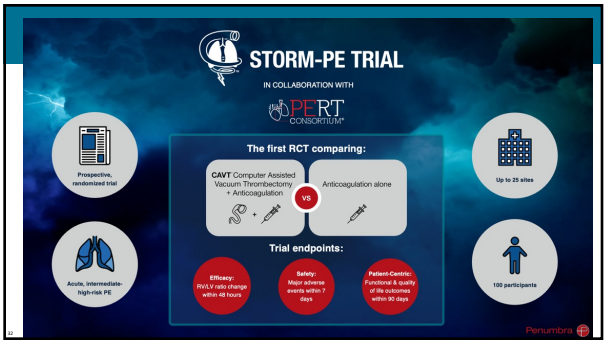
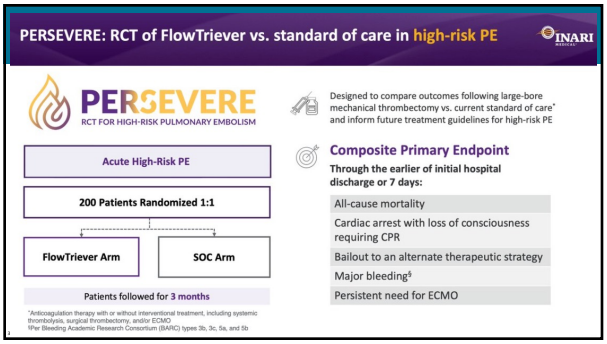
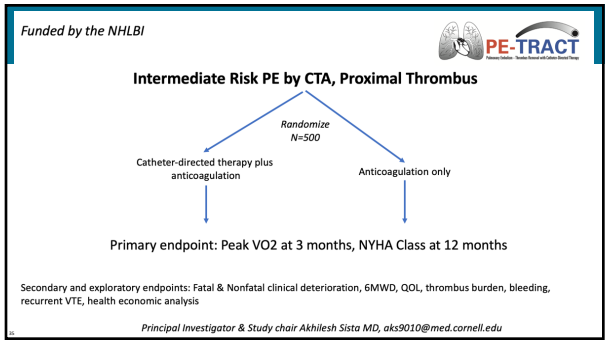
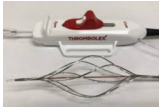






Clinical Trials

- Medical Therapy
- Catheter Directed Thrombolysis
- Catheter Directed Thrombectomy
- Pharmaco-mechanical Thrombectomy



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RAPID-PE Study

On-the-table registry of Pharmacomechanical Lysis with the BASHIR™ Endovascular Catheter for Acute Pulmonary Embolism

THROMBOLEX

Sites	Up to 50 sites
Sample Size	Up to 500 patients with intermediate-risk PE: for non-inferiority endpoints
Interim Analysis	At 50 patients: powered for superiority endpoints
Primary Endpoint	Death from any cause or hemodynamic decompensation (or collapse) through 7-day follow-up, defined as needed for cardiopulmonary resuscitation; or - SBP < 90 mmHg for at least 15 minutes; or - Drop in SBP by at least 40 mmHg for at least 15 min with signs of end-organ hypoperfusion; or - Need for catecholamine administration. to maintain adequate organ perfusion and a SBP > 90 mmHg
Secondary Endpoint	Major bleeding, as defined by ISTH: - within 72 hrs of the start of r-tPA treatment or before discharge, whichever comes first

Clinical Trials

- Medical Therapy
- Catheter Directed Thrombolysis
- Catheter Directed Thrombectomy
- Pharmaco-mechanical Thrombectomy
- Artificial Intelligence

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Artificial Intelligence: AID-PE

- **Artificial Intelligence to Improve Detection and Risk Stratification of Acute Pulmonary Embolism**
  - Patients undergoing CTPA for detection of acute PE will have imaging analyzed by **AI software in combination with a human radiologist.**
  - Researchers will compare clinical and radiology specific outcomes with a retrospective cohort of patients who have had standard routine radiology reporting.

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Currently: Six Enrolling Prospective Randomized Trials

HI-PEITHO	PE-TRACT	STORM-PE TRIAL	PEERLESS II	OPTIMO-3	PERGEVERE	PEERLESS
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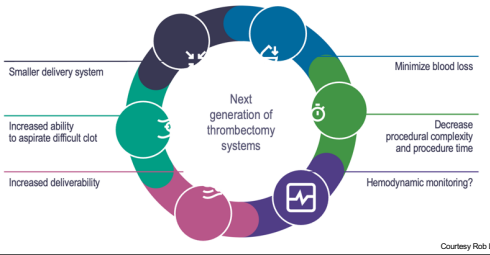
12 MONTHS	12 MONTHS	90 DAY FOLLOW UP	90 DAY FOLLOW UP	24 MONTH FOLLOW UP	90 DAY FOLLOW UP	30 DAY FOLLOW UP

Finding the Holy Grail for Aspiration Thrombectomy



Courtesy Rob Lookstein

Clinical Trial Statistics

- *Clinicaltrials.gov*: search pulmonary embolism
  - All: 857 studies
  - Recruiting or not yet recruiting: 158
  - Recruiting or not yet recruiting and device: 44

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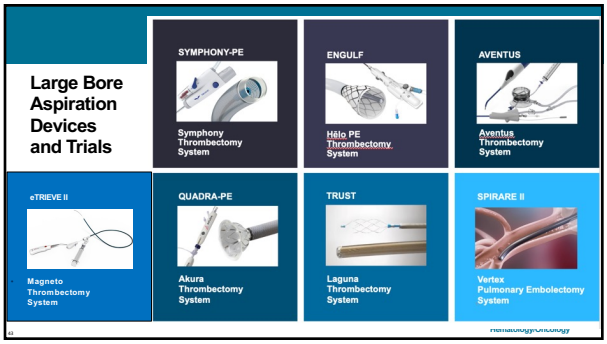
Large Bore Aspiration Devices and Trials



Many Ongoing Questions

- When to use **which** therapy for **which** patients?
  - Thromboaspiration or catheter directed thrombolysis?
    - Is there ever a role for both?
  - Is it different for INTERMEDIATE or HIGH-RISK cases?
- How do we **define success**? What are procedural end points?
  - pulmonary hemodynamics
  - vital signs
  - angiographic
  - perfusion

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Catheter Directed Therapies: Current Trials

LEVEL 1 Trials:

HI PEITHO
PEERLESS 2
PEITHO-3
PETRACT
PERSEVERE
STORM-PE

Large Bore Aspiration Devices

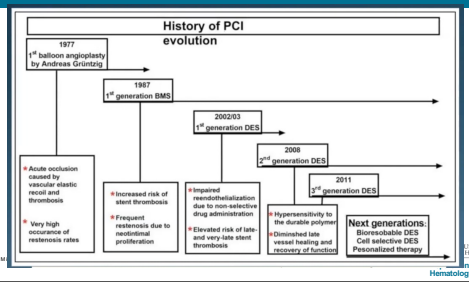
AVENTUS
ENGULF
eTREIVE II
QUADRA-PE
SPIRARE II
SYMPHONY
TRUST
RECOVER-AV

Pharmaco-mechanical Thrombectomy

RAPID-PE

Registry
Prospective
Cohort

2024



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Call to Action

- Every patient you see, consider enrolling in a prospective trial, if possible
- Data will be generated over 12-24 months from RCT and
  - May show improvements in care
  - Lead to change in guidelines
- We must continue to seek better ways to treat this disease

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Case Follow up

- He did well. Discharged home on apixaban on day 3.
- In hospital, HCT 26.8.
- Came to follow up clinic one month later, HCT still 26.8.
- Work up revealed: **Multiple Myeloma**
  - IgG 5328, IgA 22, IgM 6,
  - serum free kappa/lambda = 601/1.5 = 400 ratio
  - **M spike: 4.31 IgG Kappa**
- Just had bone marrow transplant

Importance of Follow Up Clinic

Closing Reflections

- PE is major cause of morbidity and mortality
- Endovascular therapies are taking on increasing role in therapeutic options
- We have learned a lot and moving towards better understanding, but we need much **more data** to prove what we do improves the care and benefits our patients.
- We NEED **prospective data** looking at both efficacy and safety endpoints
  - Especially for our high risk and intermediate risk patients
- Still lots of questions: which population for which device at what time?
- ENROLL
- Engage PERT (pertconsortium.org)

Thank you

@RosovskyRachel
rprosovsky@mgh.harvard.edu

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