Νεώτερες Θεραπείες Πνευμονικής Εμβολής

Αναγνωστάκος Θεοχάρης, MD PhD
Πνευμονολόγος - Φυματιολόγος
Επικ. Επιμελητής ΠΓΝ ΤΡΙΠΟΛΗΣ

Σε σχέση με την παρούσα παρουσίαση, δηλώνω ότι δεν υπάρχει οποιαδήποτε σύγκρουση συμφερόντων

2013 ESC guidelines on the Diagnosis and Management of Acute Pulmonary Embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC).

Endorsed by the European Respiratory Society (ERS).

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Management of Pulmonary Embolism

An Update

Stavros V. Konstantinides, MD, PhD,[a,b] Stefano Barco, MD,[a] Mareike Lankeit, MD,[a] Guy Meyer, MD[c]

2013 ESC guidelines on the Diagnosis and Management of Acute Pulmonary Embolism

AMERICAN COLLEGE of CARDIOLOGY

Duration of Anticoagulation Post-PE: Things to Consider

Mar 22, 2019 | Grant Senyei, MD; Timothy Fernandes, MD

Expert Analysis

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BTS guideline

British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE)

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Ghazvinian *et al. Thrombosis Journal* (2016) 14:12
DOI 10.1186/s12959-016-0086-0

Thrombosis Journal

RESEARCH Open Access

Is it safe to withhold long-term anticoagulation therapy in patients with small pulmonary emboli diagnosed by SPECT scintigraphy?

R. Ghazvinian*, A. Gottsäter and J. Elf

outpatient management of pulmonary embolism (PE)

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Is it safe to withhold long-term anticoagulation therapy in patients with small pulmonary emboli diagnosed by SPE

R. Gha

Treatment, prognosis, and follow-up of acute pulmonary embolism in adults

UpToDate 2019

Dura Things to Cons

Mar 22, 2019 | Grant Senyei, MD; Timothy Fernandes, MD

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Management of Pulmonary Embolism

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- Αιμοδυναμικά ασταθής
- Αιμοδυναμικά σταθερός
- Κατ’οίκον θεραπεία
- Θρόμβος σε υποτμηματικούς κλάδους
- Ειδικές κατηγορίες
  - Καρκινοπαθείς
  - Νεφρική ή Ηπατική ανεπάρκεια
  - Εγκυμοσύνη
- Διάρκεια θεραπείας

Αιμοδυναμικά ασταθής

Αιμοδυναμικά ασταθής

Ασθενής με υπόταση (<90mmHg για >15΄), που χρήζει χορήγηση αγγειοσυσπαστικών ή εμφανές σοκ

Acute phase treatment

Recommendations	Class	Level
PE with shock or hypotension (high risk)		
It is recommended to initiate intravenous anticoagulation with UFH without delay in patients with high-risk PE.	I	C
Thrombolytic therapy is recommended.	I	B
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.	I	C
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.	IIa	C

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Thrombolytic treatment of PE

Approved thrombolytic regimens for pulmonary embolism	
Streptokinase	250 000 IU as a loading dose over 30 minutes, followed by 100 000 IU/h over 12-24 hours.
	Accelerated regimen: 1.5 million IU over 2 hours.
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12-24 hours.
	Accelerated regimen: 3 million IU over 2 hours.
rtPA	100 mg over 2 hours; or
	0.6 mg/kg over 15 minutes (maximum dose 50 mg).

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Contraindications to thrombolysis

Absolute contraindication

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury in the preceding 3 weeks
- Gastrointestinal bleeding within the last month
- Known bleeding risk

Relative contraindications

- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within one week postpartum
- Non-compressible puncture site
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mmHg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Αιμοδυναμικά σταθερός

Acute phase treatment

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Anticoagulation - combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is ongoing.	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0-3.0).	I	B

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Acute phase treatment

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Anticoagulation - new oral anticoagulants		
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B
As an alternative to VKA treatment, administration of edoxaban is recommended following acute-phase parenteral anticoagulation.	I	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.	III	A

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Parenteral anticoagulation for PE

LMWHs and pentasaccharide (fondaparinus) approved for the treatment of pulmonary embolism		
	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg	Every 12 hours Once daily
Tinzaparin	175 U/kg	Once daily
Dalteparin	100 IU/kg or 200 IU/kg	Every 12 hours Once daily
Nadroparin	86 IU/kg or 171 IU/kg	Every 12 hours Once daily
Fondaparinux	5 mg (body weight <50 kg); 7.5 mg (body weight 50-100 kg); 10 mg (body weight >100 kg)	Once daily

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Acute phase treatment

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients without shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of rescue reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.	IIb	C
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.	IIb	B

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Venous filters

Recommendations	Class	Level
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in case of PE recurrence despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Κατ’οίκον θεραπεία

British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE)

Luke S G E Howard,[1] Steven Barden,[2] Robin Condliffe,[3] Vincent Connolly,[4] Christopher W H Davies,[5] James Donaldson,[6] Bernard Everett,[7] Catherine Free,[8] Daniel Horner,[9,10] Laura Hunter,[11] Jasvinder Kaler,[12] Catherine Nelson-Piercy,[13] Emma O'Dowd,[14] Raj Patel,[15] Wendy Preston,[16] Karen Sheares,[17] Campbell Tait[18]

. *Thorax* 2018;**73**:ii1–ii29. doi:10.1136/thoraxjnl-2018-211539

Table 3 Pulmonary Embolism Severity Index

Parameter	Score	Risk class	Total points
Demographic features		I: very low	≤65
Age	Age in years	II: low	66–85
Male sex	+10	III: intermediate	86–105
Comorbid conditions		IV: high	106–125
Cancer	+30	V: very high	≥126
Heart failure	+10		
Chronic lung disease	+10		
Clinical findings			
Pulse ≥ 110 bpm	+20		
Systolic blood pressure < 100 mm Hg	+30		
RR ≥ 30/min	+20		
Temperature < 36°C	+20		
Altered mental status*	+60		
Arterial blood oxygen saturation < 90%†	+20		

*Defined as disorientation, lethargy, stupor or coma.
†With or without the administration of supplemental oxygen.

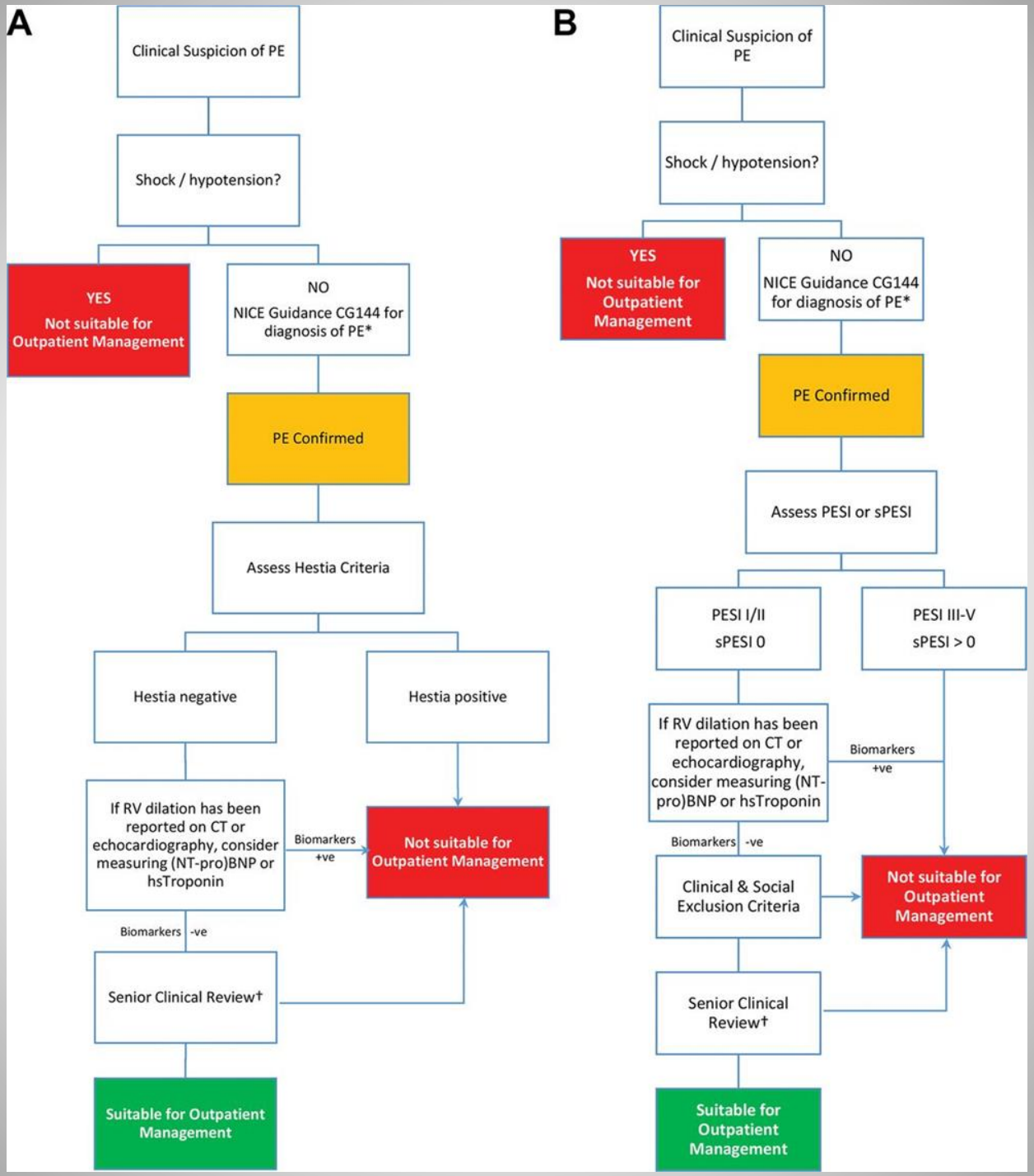
Table 4 Simplified Pulmonary Embolism Severity Index

Parameter	Score	Risk class	Total points
Age >80 years	1	Low	0
Cancer*	1	High	≥ 1
Chronic cardiopulmonary disease	1		
Pulse ≥110 bpm	1		
Systolic blood pressure < 100 mm Hg	1		
Arterial blood oxygen saturation < 90%†	1		

*Defined as active cancer (diagnosed within last 12 months or undergoing treatment, personal communication from Prof David Jimenez).
†With or without the administration of supplemental oxygen.

Hestia criteria (Zondag *et al*)[30]	
Is the patient haemodynamically unstable?*	Yes/no
Is thrombolysis or embolectomy necessary?	Yes/no
Active bleeding or high risk of bleeding?†	Yes/no
More than 24 hours of oxygen supply to maintain oxygen saturation >90%?	Yes/no
Is PE diagnosed during anticoagulant treatment?	Yes/no
Severe pain needing intravenous pain medication for >24 hours?	Yes/no
Medical or social reason for treatment in hospital >24 hours?	Yes/no
Does the patient have a creatinine clearance <30 mL/min?	Yes/no
Does the patient have severe liver impairment? (discretion of clinician)	Yes/no
Is the patient pregnant?	Yes/no
Does the patient have a documented history of heparin-induced thrombocytopenia ?	Yes/no

Eligible for outpatient treatment—no risk factors.
Ineligible for outpatient treatment—at least one risk factor present.


A
Clinical Suspicion of PE
Shock / hypotension?
YES
Not suitable for Outpatient Management
NO
NICE Guidance CG144 for diagnosis of PE*
PE Confirmed
Assess Hestia Criteria
Hestia negative
Hestia positive
If RV dilation has been reported on CT or echocardiography, consider measuring (NT-pro)BNP or hsTroponin
Biomarkers +ve
Not suitable for Outpatient Management
Biomarkers -ve
Senior Clinical Review†
Suitable for Outpatient Management
B
Clinical Suspicion of PE
Shock / hypotension?
YES
Not suitable for Outpatient Management
NO
NICE Guidance CG144 for diagnosis of PE*
PE Confirmed
Assess PESI or sPESI
PESI I/II
sPESI 0
PESI III-V
sPESI > 0
If RV dilation has been reported on CT or echocardiography, consider measuring (NT-pro)BNP or hsTroponin
Biomarkers +ve
Biomarkers -ve
Clinical & Social Exclusion Criteria
Not suitable for Outpatient Management
Senior Clinical Review†
Suitable for Outpatient Management

Box 1 Clinical exclusion criteria[8]

- Oxygen saturation <90%
- Systolic blood pressure <100 mm Hg
- Chest pain needing opiates
- Active bleeding
- High risk of bleeding (stroke within the preceding 10 days, gastrointestinal bleed within the last 14 days or platelet count <75 000/mm^3)
- Obesity (weight >150 kg)
- Heparin-induced thrombocytopenia
- Severe renal failure (creatinine clearance <30 mL/min)
- Therapeutic anticoagulation (International Normalised Ratio ≥2.0) at diagnosis
- Barriers to treatment adherence or follow-up

Social reasons which may include inability to return home, inadequate care at home, lack of telephone communication, concerns over compliance, etc.

Outcomes of outpatient care for low-risk pulmonary embolism (PE)

Recommendations

- Patients with PE should be assessed for suitability for management as outpatients (OPs). Grade B
- Patients assessed as low risk and suitable for OP management should be offered treatment in an OP setting where a robust pathway exists for follow-up and monitoring. Grade B

Θρόμβος σε υπό-τμηματικούς κλάδους

Ghazvinian *et al. Thrombosis Journal* (2016) 14:12
DOI 10.1186/s12959-016-0086-0

Thrombosis Journal

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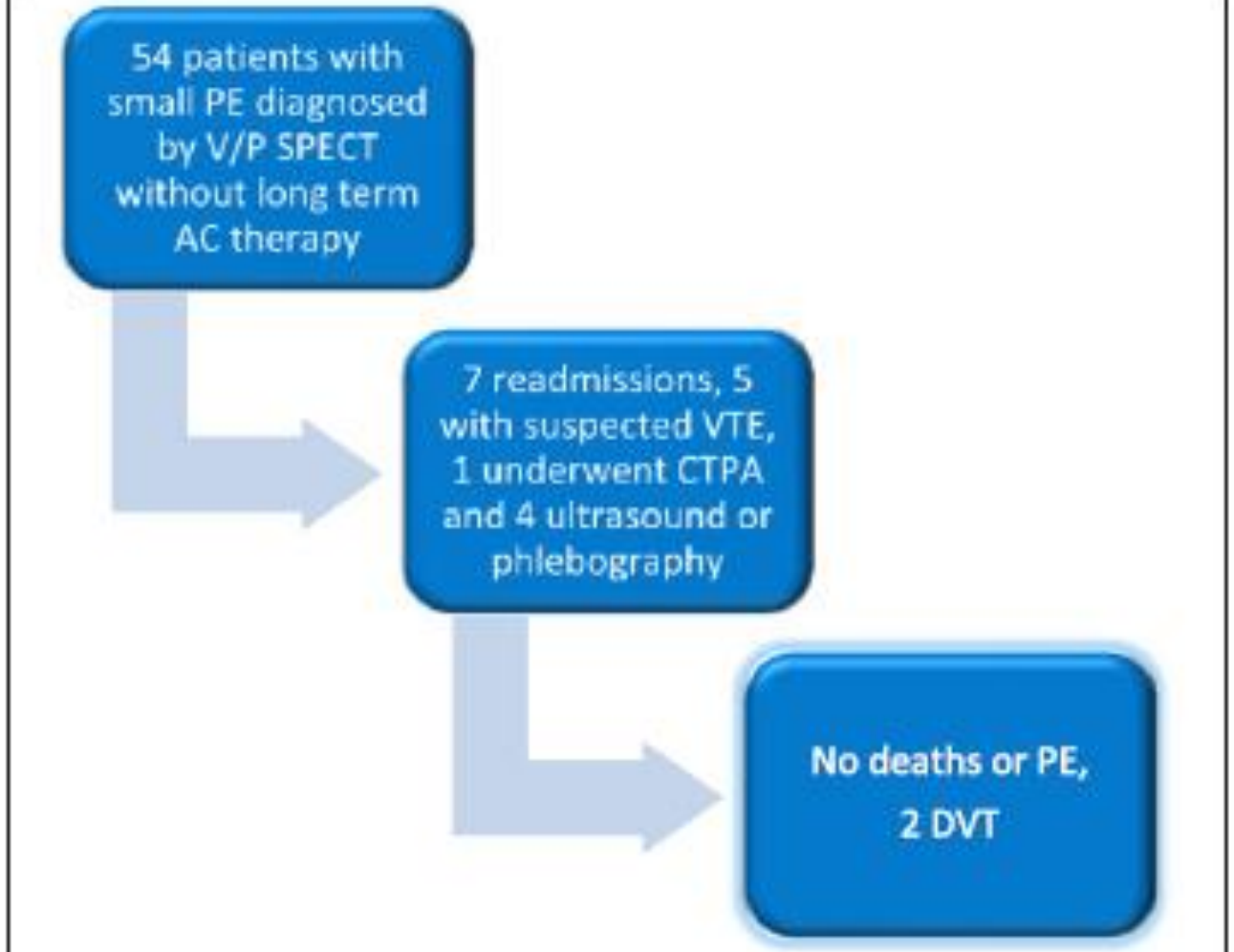


Fig. 1 Flow diagram of study. PE = Pulmonary embolism, V/P SPECT = Ventilation/Perfusion single photon emission computed tomography, AC = Anticoagulant, VTE = Venous thromboembolism, CTPA = Computed tomography pulmonary angiography, DVT = Deep vein thrombosis

Conclusions

Withholding of conventional long term AC therapy in patients diagnosed with small PE with V/P SPECT was associated with a 4 % risk of VTE diagnosis during 3 months of follow-up. This would not be considered acceptable for the majority of clinicians, and the concept can at the present stage therefore not be recommended.

Διάρκεια θεραπείας

Duration of treatment

Recommendations	Class	Level
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.	IIa	B
In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.	IIb	B

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

AMERICAN COLLEGE of CARDIOLOGY

Duration of Anticoagulation Post-PE: Things to Consider

Mar 22, 2019 | Grant Senyei, MD; Timothy Fernandes, MD

Expert Analysis

Identifying Provoked vs. Unprovoked PE

Provoked Conditions
Major surgery with general anesthesia >30 minutes
Pregnancy, particularly with cesarean delivery
Lower limb plaster cast
Short-term immobilization for >3 days
Prolonged air travel for >12 hours
Hormonal contraception
Hormone replacement therapy
Acute infectious disease
Direct trauma to the leg

Unprovoked or Persistent Risk Factors
Collagen vascular diseases
Antiphospholipid syndrome
Active cancer
Myeloproliferative disorders
Thrombophilia

Current guidelines recommend patients with provoked PE or those with transient risk factors, such as major surgery or immobilization, be treated for a duration of 3 months. This is driven by the fact that the risk for recurrent VTE in these patients is 1% in the first year after stopping anticoagulation and 0.5% per year after.[2] As long as patients with provoked PE return to their pre-PE baseline,

indefinite anticoagulation is recommended in those patients with unprovoked PE or persistent risk factors. In those with unprovoked PE who elect to stop indefinite anticoagulation, the risk for recurrent VTE is 10% in the first year after stopping anticoagulation and 5% per year after.[2] Although indefinite treatment is recommended in these patients, it is important to reassess the risks and benefits of ongoing anticoagulation at regular intervals.

2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315-52.

RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Guidelines for the Diagnosis, Treatment, and Follow up of Pulmonary Embolism

Duration of Secondary Prophylaxis in Pulmonary Embolism*

6 months	Transient risk factors First idiopathic episode not severe, without markers indicative of recurrence during follow up (thrombophilia, occult cancer, residual venous thrombosis, elevated D-dimer levels)
Long term†	Persistent risk factors First idiopathic episode severe or with markers indicative of recurrence during follow up Second episode

*Risk of bleeding conditions duration on a case –by– case basis.
†The duration of long-term prophylaxis has not been established. In many cases, after individual assessment, treatment continues indefinitely.

Ειδικές κατηγορίες

Εγκυμοσύνη

PE in pregnancy

Recommendations	Class	Level
Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.	I	C
D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients.	IIb	C
Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE.	IIb	C
Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal chest X-ray.	IIb	C
CT angiography should be considered if the chest X-ray is abnormal or if lung scintigraphy is not readily available.	IIa	C
A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension.	I	B

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Καρκινοπαθείς

PE in cancer

Recommendations	Class	Level
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3 to 6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3 to 6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

Antithrombotic therapy for venous thromboembolism in patients with cancer: expert guidance

Davide Imberti, Claudio Cimminiello, Marcello Di Nisio, Marco Marietta, Hernan Polo Friz & Walter Ageno

EXPERT OPINION ON PHARMACOTHERAPY
2018, VOL. 19, NO. 11, 1177–1185
https://doi.org/10.1080/14656566.2018.1496238

Expert opinion: Based on the available evidence, DOACs represent a valid alternative to LMWH for the treatment of CAT for the majority of patients with active cancer. Currently, most solid evidence comes from the Hokusai VTE-cancer study, which showed that edoxaban is non-inferior to the LMWH dalteparin, with a trend toward fewer recurrent venous thromboembolic events, but with more major bleeding events. Similar findings were reported with rivaroxaban, although the study was not sufficiently powered to allow definitive conclusions. The majority of bleeding events occurred in the upper gastrointestinal tract and in patients with gastrointestinal cancer. Thus, LMWH remains the preferred option for patients with gastrointestinal cancer. Additional studies aimed to confirm these findings with other DOACs are now warranted.

Νεφρική ή Ηπατική ανεπάρκεια

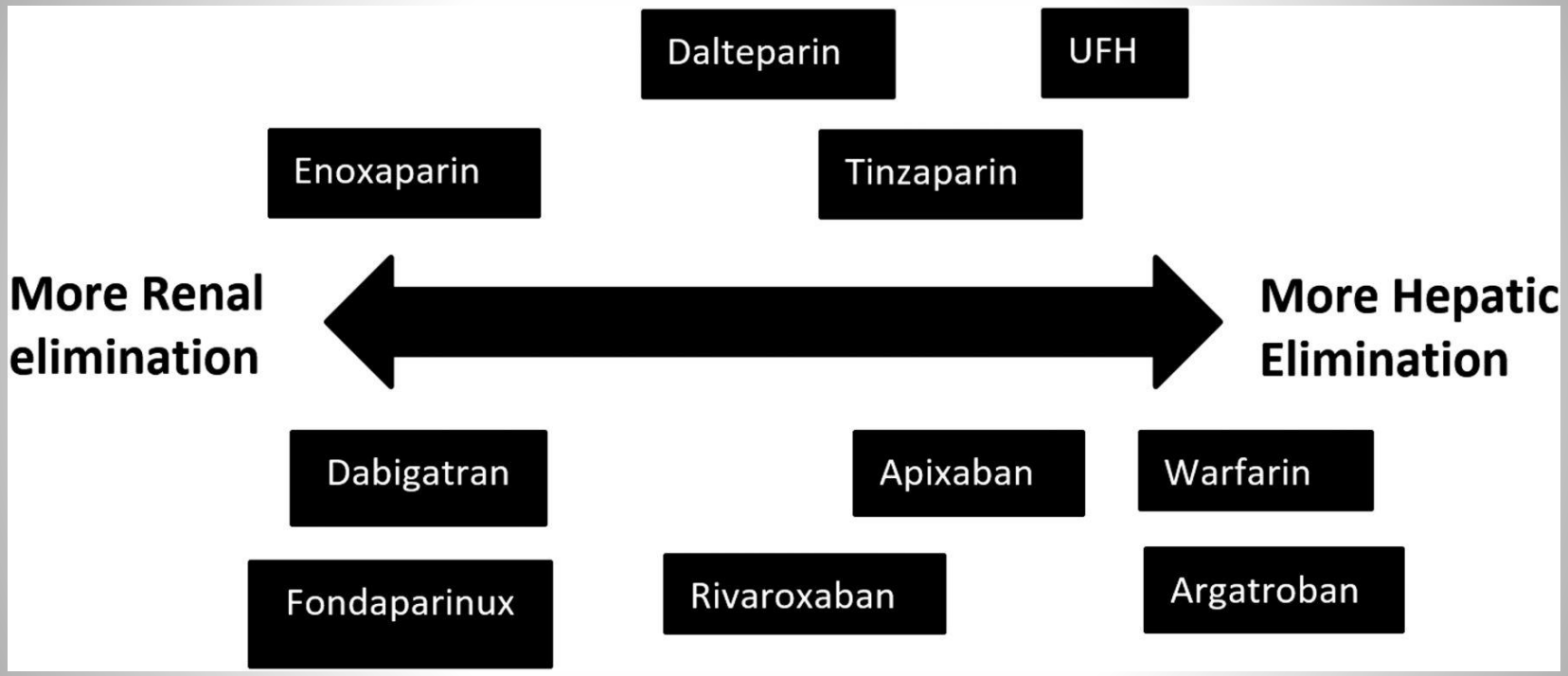
Thrombosis and anticoagulation in the setting of renal or liver disease

Christine Ribic and Mark Crowther

Department of Medicine and Department of Pathology and Molecular Medicine, McMaster University, and St Joseph's Healthcare, Hamilton, ON, Canada

Hematology 2016

Renal and hepatic dependency of drugs discussed.



Christine Ribic, and Mark Crowther Hematology 2016;2016:188-195

Table 1. Evidence for use of anticoagulant class according to renal function

eGFR (mL/min)	UFH	LMWHs	Warfarin	Direct oral anticoagulants
>90	Yes	Yes	Yes	Yes
60-89	Yes	Yes	Yes	Yes
30-59	Yes	Yes	Yes	Rivaroxaban dose adjustment
15-29	Yes	Dose adjustments may be needed; bioaccumulation possible Enoxaparin use with caution	Yes	Rivaroxaban and dabigatran contraindicated Apixaban use with caution
<15	Yes	Use contraindicated outside selected patients with appropriate monitoring	Yes	Rivaroxaban and dabigatran contraindicated; see text for discussion of apixaban

Yes indicates there is evidence for use without dose adjustment.

Direct thrombin inhibitors

Dabigatran

Directly and reversibly inhibits thrombin preventing conversion of fibrinogen to fibrin and limiting thrombin-mediated platelet aggregation

No dosage adjustments in the setting of liver disease

Not recommended in patients with severe impairment (Child-Pugh class C), acute liver disease, or increased liver enzymes 2 or more times the upper limit of normal

Argatroban

It is cleared independent of renal function and can be used across the range of renal function

ΑΝΤΙΔΟΤΑ

ΑΝΤΙΔΟΤΑ

Currently, only one specific antidote, idarucizumab, is licensed for use and is indicated to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery.

ΑΝΤΙΔΟΤΑ

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 March 2019
Media and Public Relations

Press release

First antidote for reversal of anticoagulation with factor Xa inhibitors apixaban and rivaroxaban

The opinion adopted by the CHMP at its February 2019 meeting is an intermediary step on Ondexxya's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

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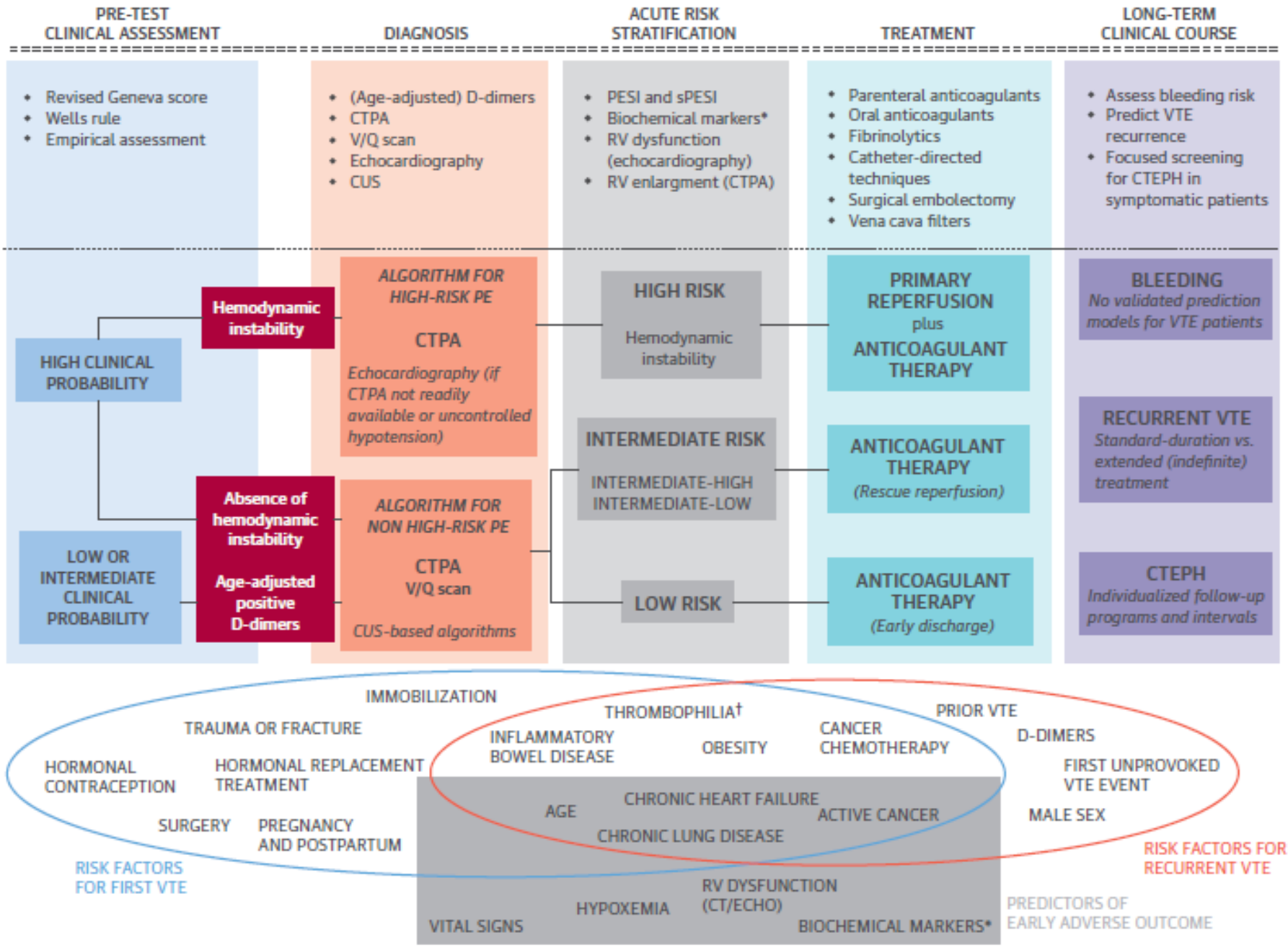
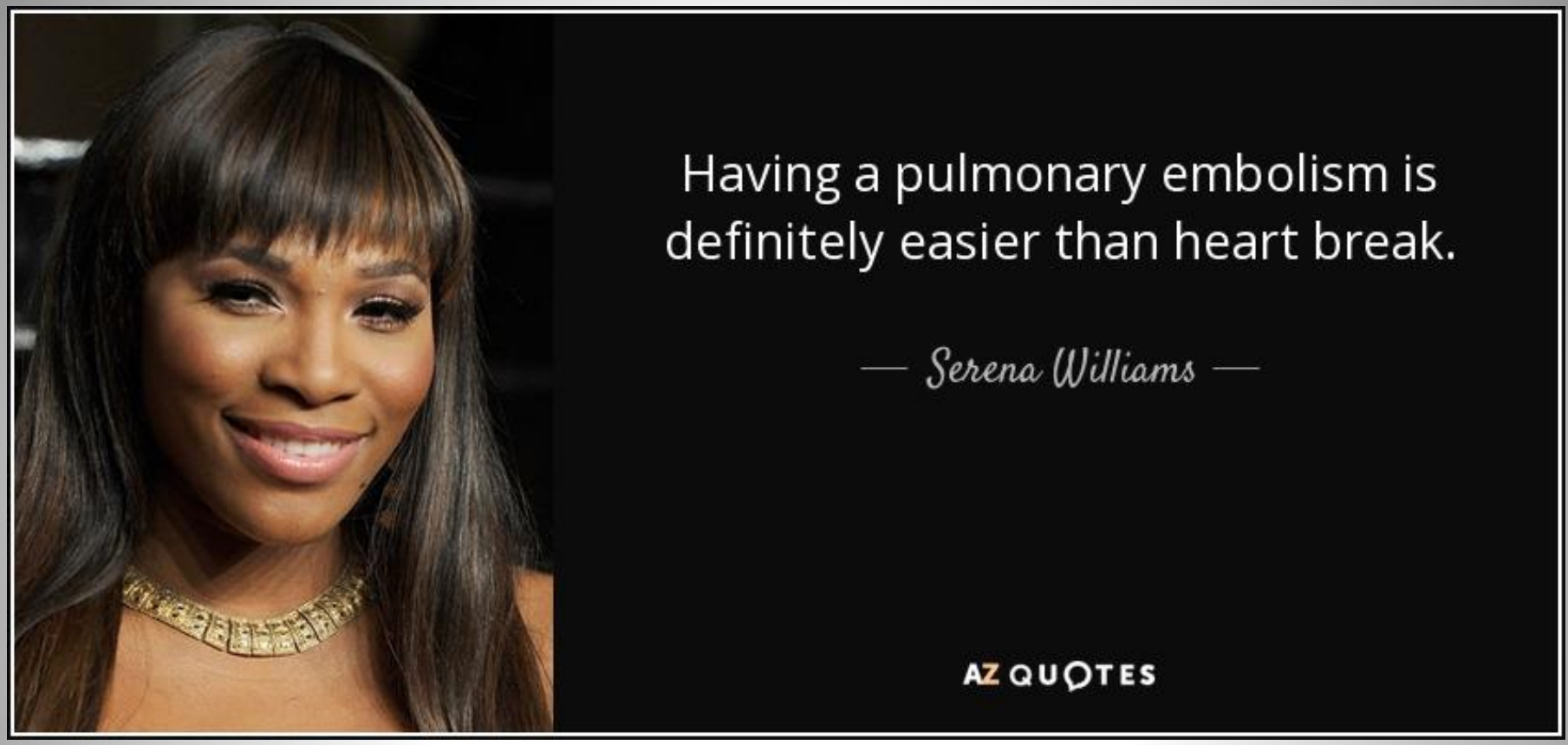
FIGURE 1 **PE: Risk-Adjusted Management in the Acute Phase and Over the Long Term**




SERENA WILLIAMS & EMBOLISM DURING CHILDBIRTH
WHAT YOU SHOULD KNOW ABOUT EMBOLISMS
MORNING NEWS
KTLA 5
TRAFFIC
arbara, Sheffield Dr At Ortega Hill Rd - Flooding - road closed - due to mudslides
60°
10:37A


Having a pulmonary embolism is definitely easier than heart break.
— Serena Williams —
AZ QUOTES

ΚΑΛΟ ΚΑΛΟΚΑΙΡΙ