Paclitaxel-related mortality

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Disclosures

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SYSTEMATIC REVIEW AND META-ANALYSIS

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSc, EBIR; Stavros Spiliopoulos, MD, PhD; Panagiotis Kitrou, MD, PhD; Miltiadis Krokidis, MD, PhD; Dimitrios Karnabatidis, MD, PhD

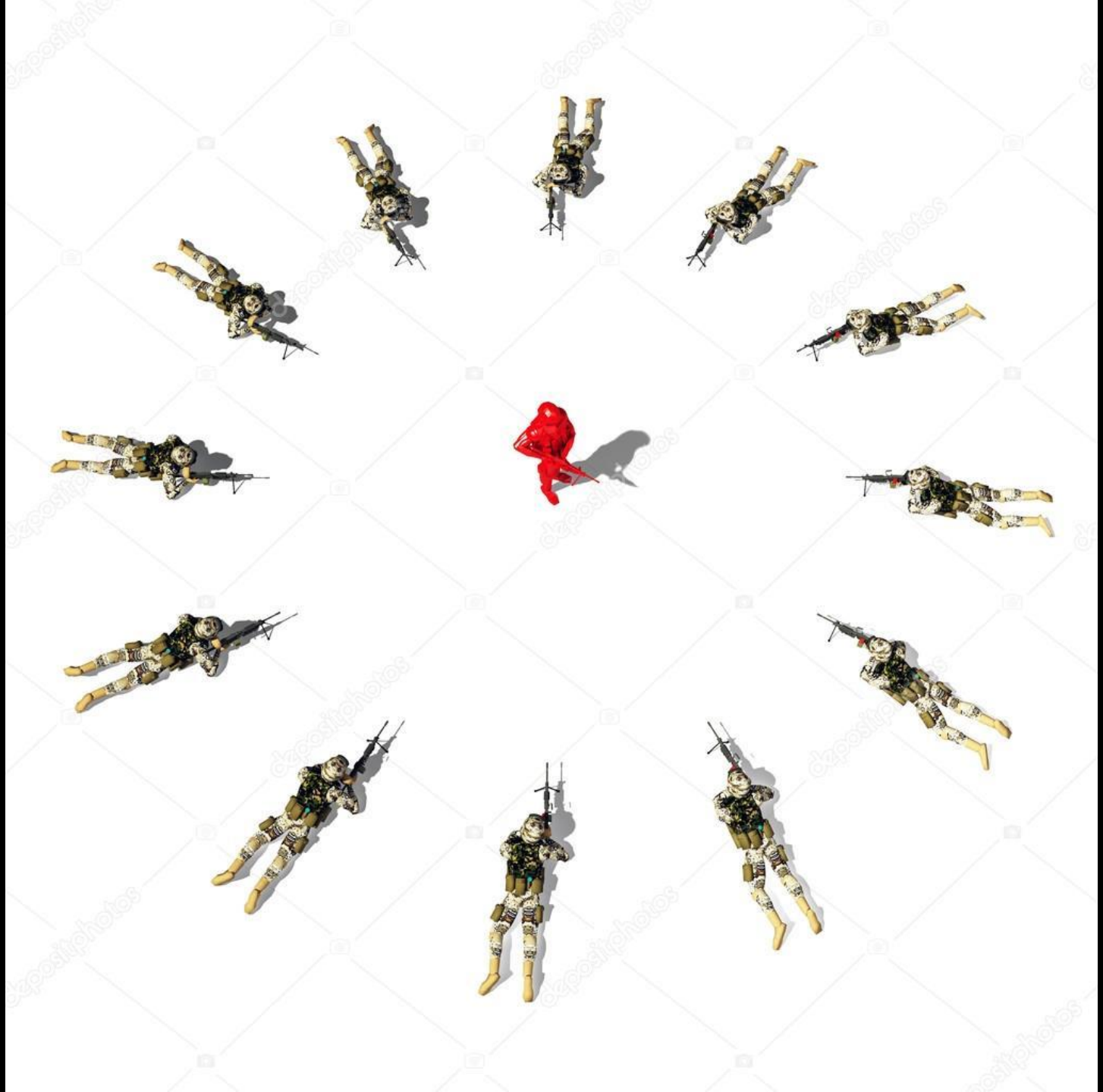
Background—Several randomized controlled trials (RCTs) have already shown that paclitaxel-coated balloons and stents significantly reduce the rates of vessel restenosis and target lesion revascularization after lower extremity interventions.

Methods and Results—A systematic review and meta-analysis of RCTs investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed. The primary safety measure was all-cause patient death. Risk ratios and risk differences were pooled with a random effects model. In all, 28 RCTs with 4663 patients (89% intermittent claudication) were analyzed. All-cause patient death at 1 year (28 RCTs with 4432 cases) was similar between paclitaxel-coated devices and control arms (2.3% versus 2.3% crude risk of death; risk ratio, 1.08; 95% CI, 0.72–1.61). All-cause death at 2 years (12 RCTs with 2316 cases) was significantly increased in the case of paclitaxel versus control (7.2% versus 3.8% crude risk of death; risk ratio, 1.68; 95% CI, 1.15–2.47; —number-needed-to-harm, 29 patients [95% CI, 19–59]). All-cause death up to 5 years (3 RCTs with 863 cases) increased further in the case of paclitaxel (14.7% versus 8.1% crude risk of death; risk ratio, 1.93; 95% CI, 1.27–2.93; —number-needed-to-harm, 14 patients [95% CI, 9–32]). Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; $P<0.001$). Trial sequential analysis excluded false-positive findings with 99% certainty (2-sided α, 1.0%).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Clinical Trial Registration—URL: www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42018099447. **(*J Am Heart Assoc.* 2018;7:e011245. DOI: 10.1161/JAHA.118.011245.)**

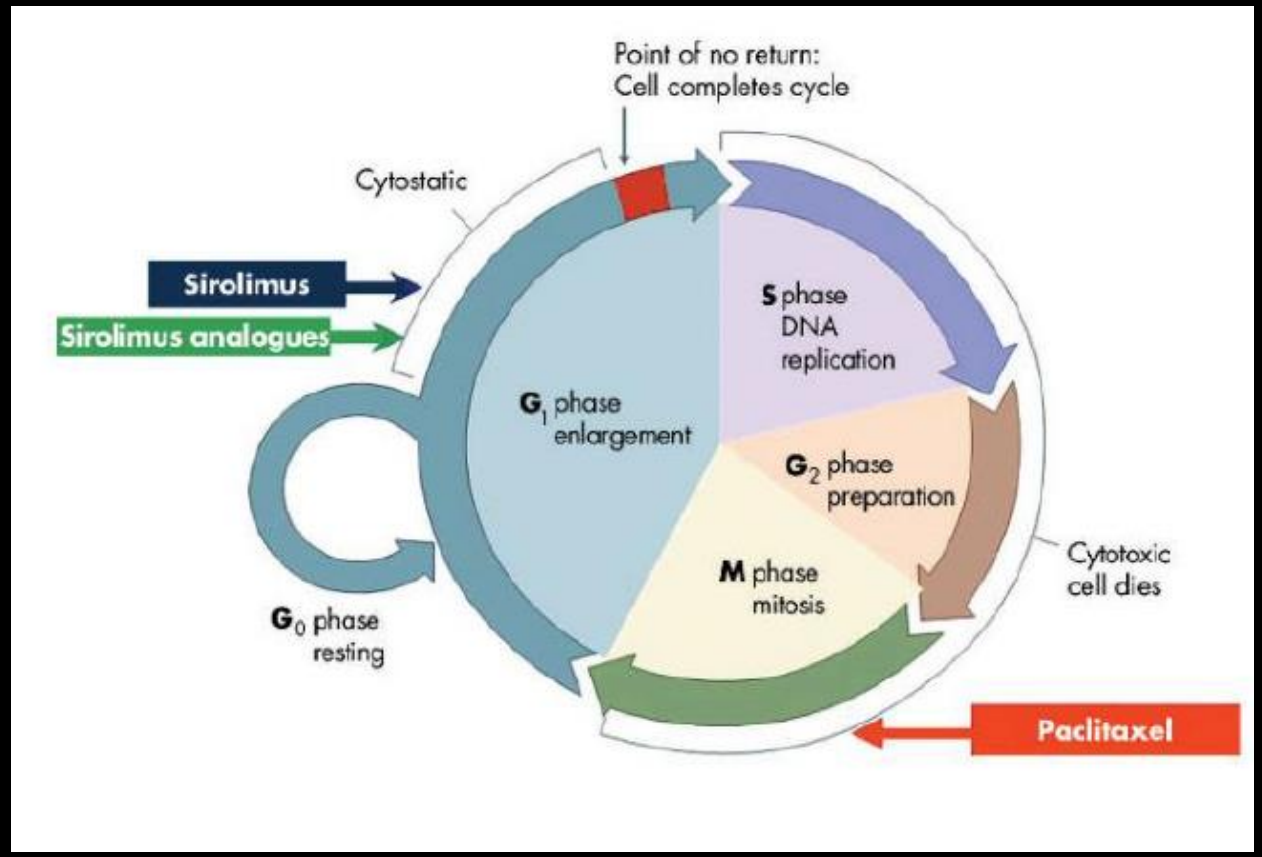
Key Words: balloon angioplasty • paclitaxel • paclitaxel-coated balloon • paclitaxel-eluting stent



PTX

PTX

Anticancer cytotoxic agent that blocks cell proliferation by binding to intracellular tubulin and interfering with spindle formation and disassembly

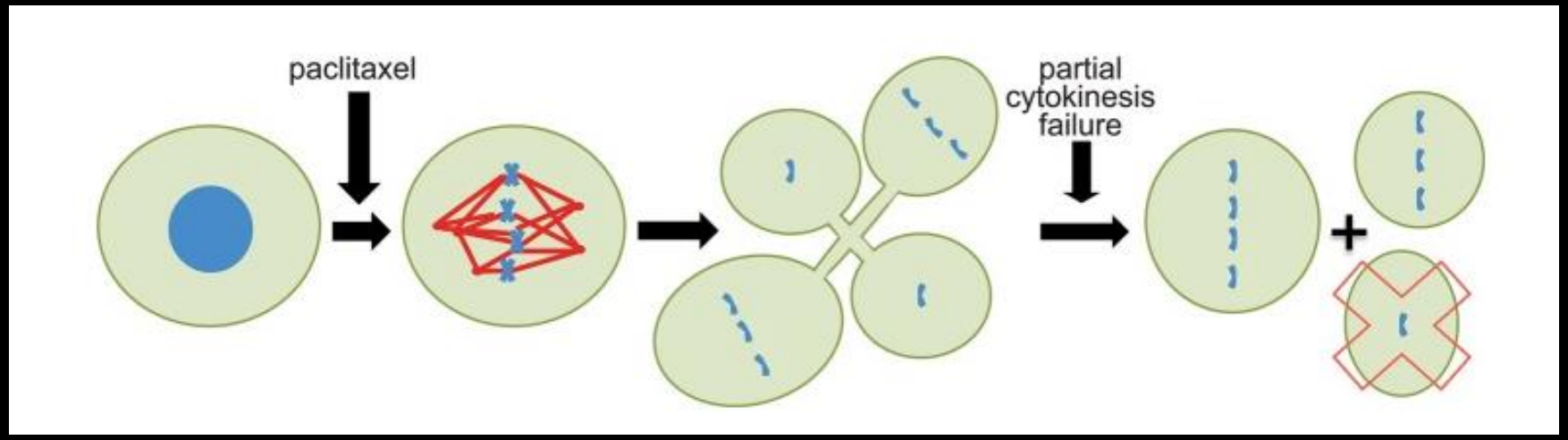


Horwitz SB. Taxol (paclitaxel): mechanisms of action. Annals of oncology : official journal of the European Society for Medical Oncology. 1994;5 Suppl 6:S3-6.

What about “low-dose” PTX

Intratumoral concentrations of paclitaxel are too low to cause mitotic arrest and result in multipolar divisions instead.

The resultant daughter cells are aneuploid or polyploid.



Weaver BA, How Taxol/paclitaxel kills cancer cells
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PTX in DCBs compared to Chemo

Chemo PTX: Half-life of 6-12 hours

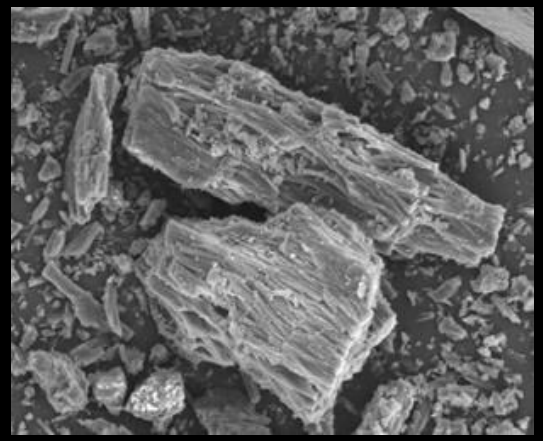
PTX in DCBs:

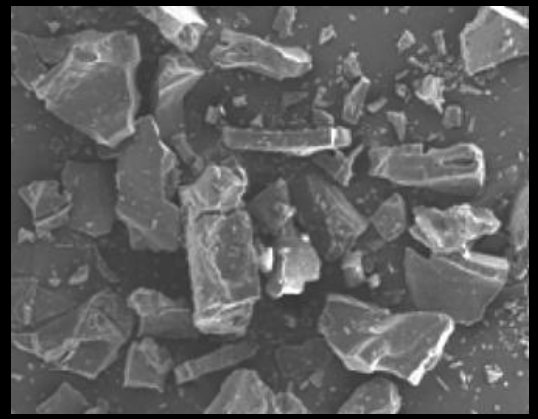
Crystallin form + Excipient

3-5% goes to the vascular wall

as high as 90% escapes to circulation

In animal models, PTX was detected in muscles of the lower limbs, in the lungs and in the liver at decreasing doses up to 18 months later





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PTX in SFA

PTX in SFA

SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association | American Stroke Association

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Cardiovasc Intervent Radiol (2020) 43:20–22
https://doi.org/10.1007/s00270-019-02390-8

CIRSE

Check for updates

COMMENTARY

Paclitaxel in Peripheral Vascular Disease: Guilty Until Proven Innocent

Konstantinos Katsanos[1] · Panagiotis Kitrou[1] · Stavros Spiliopoulos[2] · Miltiadis Krokidis[3] · Dimitrios Karnabatidis[1]

PTX in SFA

Study-level meta-analysis that demonstrated a significantly higher long-term risk of death with the application of paclitaxel in the femoropopliteal artery in the lower limbs

Latest update:

19 studies encompassing 3386 cases were pooled at 2 years.

4.7% crude risk of death

Pooled RR was 1.42 (95% CI 1.05–1.92; P = 0.02).

5 studies including 1429 cases were pooled at 5 years.

10.4% crude risk of death

Pooled RR was 1.64 (95% CI 1.22–2.20; P = 0.0009)

Response to Letter by Bonassi on Article "Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials". Katsanos et al. J Am Heart Assoc. 2019 May 21;8(10):e012172. doi: 10.1161/JAHA.119.012172

PTX in BTK

PTX in BTK

EVIDENCE-BASED REVIEW

Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, MSc, PhD, Stavros Spiliopoulos, MD, PhD, Panagiotis Kitrou, MD, PhD, Miltiadis Krokidis, MD, PhD, Ioannis Paraskevopoulos, MD, PhD, and Dimitrios Karnabatidis, MD, PhD

Katsanos et al. Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Vasc Interv Radiol. 2020 Jan 8. pii: S1051-0443(19)30955-8. doi: 10.1016/j.jvir.2019.11.015.

PTX in BTK

PCBs for BTK lesions in CLI patients

Study-level meta-analysis of RCTs

- 8 randomized controlled trials
- 1,420 patients (97% CLI)
- Up to 1-year follow-up.

Primary Efficacy endpoint:

- AFS: freedom from all-cause death and major amputation

Secondary Efficacy Endpoint:

- TLR

Katsanos et al. Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Vasc Interv Radiol. 2020 Jan 8. pii: S1051-0443(19)30955-8. doi: 10.1016/j.jvir.2019.11.015.

PTX in BTK

AFS was significantly worse in case of PTX

13.7% crude risk of death or limb loss compared to 9.4% in case of PTA;
hazard ratio 1.52; 95% confidence interval: 1.12–2.07, p= .008

TLR was significantly reduced in case of PTX

11.8% crude risk of TLR versus 25.6% in control;
risk ratio 0.53; 95% confidence interval: 0.35–0.81, p= .004

The harm signal was evident when examining the high-dose (3.0-3.5 µg/mm2) devices but attenuated below significance in case of a low-dose (2.0 µg/mm2) device.

Katsanos et al. Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Vasc Interv Radiol. 2020 Jan 8. pii: S1051-0443(19)30955-8. doi: 10.1016/j.jvir.2019.11.015.

What about PTX in AV?

What about PTX in AV?

High mortality rate of this population: up to 33% at 2 years

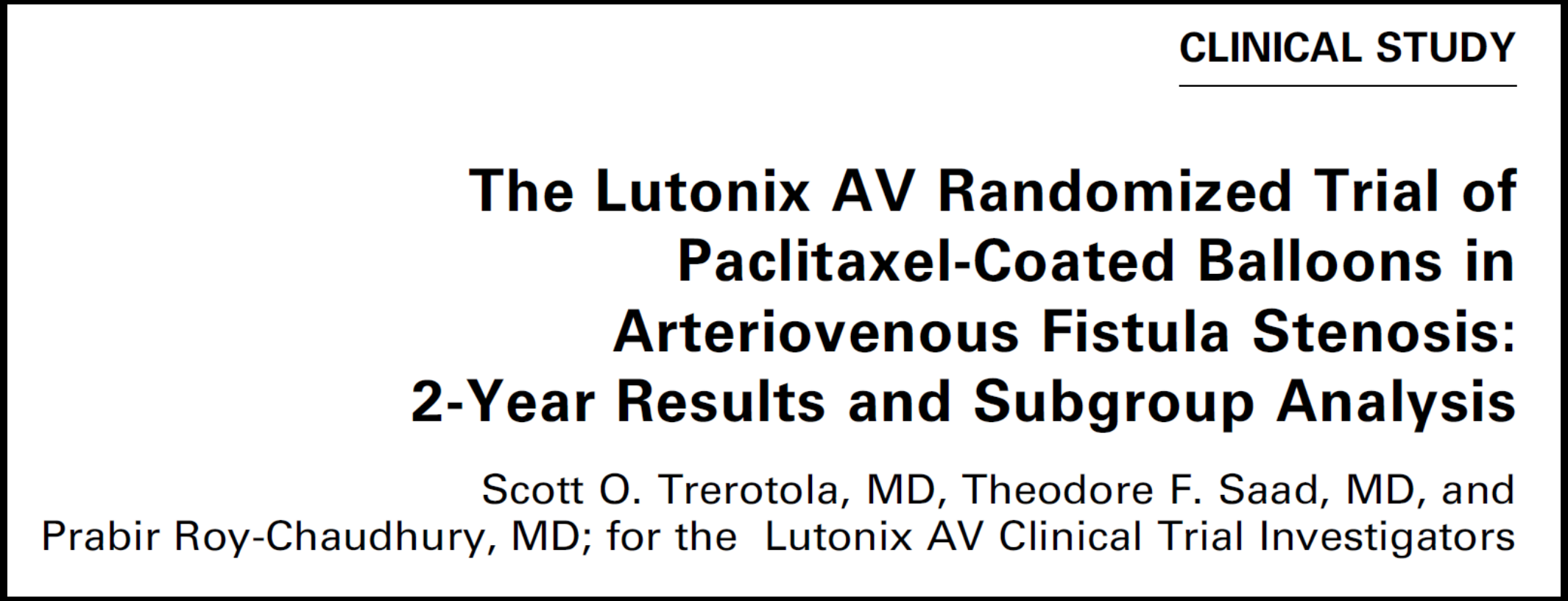
Much more comorbidities compared to SFA

Lower dose of PTX compared to SFA

Much shorter lesions compared to SFA

USRDS 2018 Chapter 5 Mortality, Table 5.3

What about PTX in AV?



CLINICAL STUDY

The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis

Scott O. Trerotola, MD, Theodore F. Saad, MD, and Prabir Roy-Chaudhury, MD; for the Lutonix AV Clinical Trial Investigators

Trerotola at el. Is the only available RCT so far with results of up to 2 years. No significant difference in mortality between the two groups p=0.27

Trerotola et al. The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis. J Vasc Interv Radiol. 2020 Jan;31(1):1-14.e5. doi: 10.1016/j.jvir.2019.08.035. Epub 2019 Nov 6

What about PTX in AV?

Big multi-center RCTs are on the way to provide additional data

- **INPACT AV** (1-year results will be presented during LINC)
- **PAVE study** (6-month results will be presented during LINC)
- **ABISS trial** (Recruitment is almost finished)

Maybe previous RCTs should also publish their long-term data in terms of safety

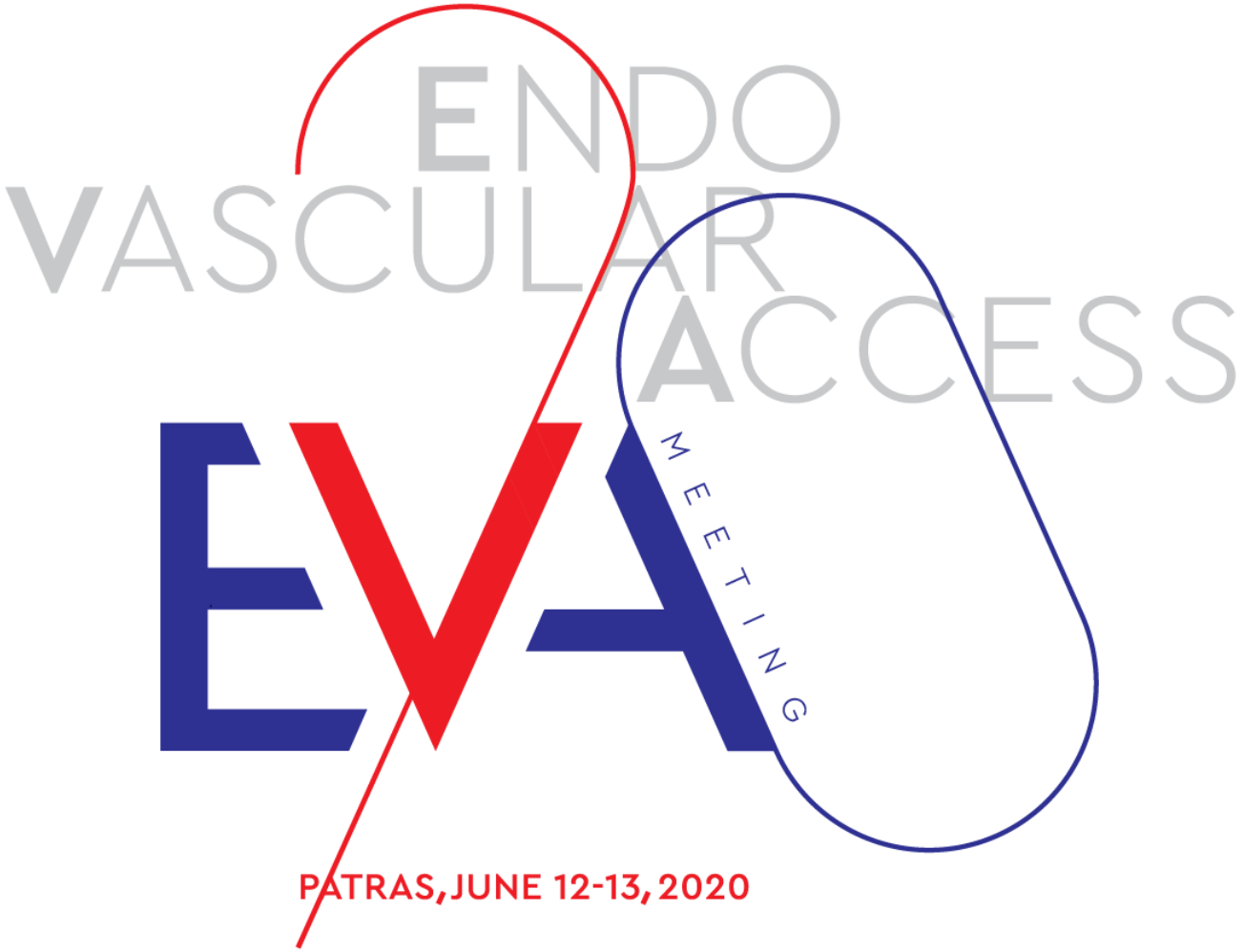
Number will hardly exceed 1,000 pts in RCTs

What about PTX in AV?

No data, at the moment, to justify concern

In such a high risk and high mortality population, the benefits from the use of DCBs would outweigh the risks and offer quality of life to the patients

More data is needed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