

Terence K. Trow, MD

Director, Pulmonary Vascular Disease Program

Yale University School of Medicine

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Medical Therapy for Chronic Thromboembolic Pulmonary Hypertension

General Reviews:

1. Lang IM, Kleptko W. Chronic thromboembolic pulmonary hypertension: an updated review. *Cur Opin Cardiol* 2008; 23:555-559.
2. Bresser P, Pepke-Zaba J, Humbert M, Hoeper M. Medical therapy for chronic thromboembolic pulmonary hypertension *Proc Am Thor Soc* 2006; 3:594-600.
3. Auger WR, Fedullo P. Chronic thromboembolic pulmonary hypertension. *Seminars in Resp and Crit Care Med* 2009; 30(4):471-483.

An excellent and comprehensive discussion of the topic with a very up-to-date summary of what we know as of 2009 on medical therapies.

Microvascular Disease:

4. Galie N, Kim HSN. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. *Proc Am Thor Soc* 2006; 3:571-576.

A well written discussion of the type of microvascular disease that can complicate CTEPH and it's impact on outcome.

5. Moser KM, Bloom CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. *Chest* 1993; 103:685-92.

A Possible Role for Endothelin-1 in CTEPH:

6. **Kim H, Yung GL, Marsh JJ, et al. Pulmonary vascular remodeling distal to pulmonary artery ligation is accompanied by upregulation of endothelin receptors and nitric oxide synthase. *Exp Lung Res* 2000; 26:287-301.**
7. **Kim H, Yung GL, Marsh JJ, et al. Endothelin mediates pulmonary vascular remodeling in a canine model of chronic embolic pulmonary hypertension. *Eur Resp J* 2000; 15:640-648.**
8. **Bauer M, Wilkens H, Langer F, et al. Selective upregulation of endothelin B receptor gene expression in severe pulmonary hypertension. *Circ* 2002; 105:1034-1036.**
9. **Reesink HJ, Meijer RC, Lutter R, et al. Hemodynamic and clinical correlates of endothelin-1 in chronic thromboembolic pulmonary hypertension. *Circ J* 2006; 70:1058-1063.**

Bosentan to Treat CTEPH:

10. **Hughes R, George P, Parameshwar J, et al. Bosentan in inoperable chronic thromboembolic pulmonary hypertension. *Thorax* 2005; 60(8):707.**
11. **Bonderman D, Nowotny R, Skoro-Sajer N, et al. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; 128:2599-2603.**
12. **Hoepfer MM, Kramm T, Wilkens H, et al. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2005; 128:2363-2367.**

References 11 & 12 represent the first open label trials of bosentan in CTEPH in 11 and 19 patients respectively and hint at therapeutic benefit in 6 MWD, PVR, NT-proBNP, and functional class. These must be interpreted with caution given the small, unblinded nature of the trials and the potential for "placebo" effect.

13. **Segovia C, Ortiz U, Bueno G, et al. Role of bosentan in patients with chronic venous thromboembolic pulmonary hypertension. *Med Clin (Barc)* 2007; 128(1):12-14.**
14. **Kourouklis S, Christopoulos A, Liagkas K, et al. Bosentan in Eisenmenger syndrome and chronic thromboembolic pulmonary hypertension. *Eur J Clin Invest* 2006; 36(suppl. 3):39-43.**
15. **Hughes RJ, Jais X, Bonderman D, et al. The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. *Eur Resp J* 2006;**

28:138-143.

16. **Seyfarth JJ, Hammerschmidt S, Pankau H, et al. Long-term bosentan in chronic thromboembolic pulmonary hypertension. *Respiration* 2007; 74:287-292.**

References 15 and 16 extend the observations made in references 11 & 12 by looking at 1-2 year experiences. Again, these are unblinded open label trials that must be viewed as hypothesis generating.

17. **Ulrich S, Speich R, Domenighetti G, et al. Bosentan therapy for chronic thromboembolic pulmonary hypertension. *Swiss Med Wkly* 2007; 137:573-580.**
18. **Vassallo FG, Kodric M, Scarduelli C, et al. Bosentan for patients with chronic thromboembolic pulmonary hypertension. *Eur J Int Med* 2009; 20:24-29.**
19. **Jais X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension (BENEFiT trial). 2008; *J Am Coll Cardiol* ; 52:2127-2134.**

The first randomized, blinded placebo controlled trial of bosentan in 157 patients with CTEPH. While PVR, TPR, NT-proBNP, and cardiac index all improved in the treatment group suggesting therapeutic effect, 6 MWD did not improve for unclear reasons.

20. **Reesink HJ, Surie S, Klock JJ, et al. Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg* 2009; (in press):1-7.**

A Role for Nitric Oxide Synthase in CTEPH:

21. **Fadel E, Mazmanian GM, Baudet B, et al. Endothelial nitric oxide synthase function in pig lung after chronic pulmonary artery obstruction. *Am J Resp Crit Care Med* 2000; 162:1429-1434.**

In this piglet model, eNOS mRNA transcripts and protein were decreased after chronic occlusion of the pulmonary artery.

Sildenafil in CTEPH:

22. **Suntharalingam J, Hughes RJ, Goldsmith K, et al. Acute haemodynamic responses to inhaled nitric oxide and intravenous sildenafil in distal chronic thromboembolic pulmonary hypertension. *Vasc Pharm* 2007; 46: 449-455.**

Acutely, IV sildenafil did have significant vasodilatory effects in 9 patients, and consistently more so than nitric oxide.

23. **Ghofrani HA, Schermuly RT, Rose F, et al. Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. *Am J Resp Crit Care Med* 2003; 167:1139-1141.**
24. **Sheth A, Park JES, Ong YE, et al. Early hemodynamic benefit of sildenafil in patients with coexisting chronic thromboembolic pulmonary hypertension. *Vasc Pharm* 2005; 42:41-45.**
25. **Rossi R, Nuzzo A, Lattanzi, et al. Sildenafil improves endothelial function in patients with pulmonary hypertension. *Pulm Pharmacol & Therap* 2008; 21:172-177.**
26. **Chapman TH, Wilde M, Sheth A, Madden BP. Sildenafil therapy in secondary pulmonary hypertension: is there benefit in prolonged use? *Vasc Pharma* 2009; 51:90-95.**

All of these references are small open label uncontrolled short term studies implying benefit in either 6MWD, PVR, echocardiography criteria (e.g Tei index), or functional class. The signals seen warrant a formal controlled trial yet to be offered in the literature. The study by Chapman combines many secondary forms of PH making specific statements about CTEPH difficult.

27. **Reichenberger F, Voswinckel R, Enke B, et al. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. *Eur Resp J* 2007; 30:922-927.**
28. **Suntharalingam J, Treacy C, Doughty NJ, et al. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest* 2008; 134:29-236.**

These open label studies of 104 and 19 patients respectively examine effects over 12 months or longer. While the Reichenberger study (open label) did show significant 6 MWD improvements and PVR improvements, the Suntharalingam study did not show 6 MWD improvements but may have been underpowered to do so. In the later study a blinded 3 months randomized placebo control period was followed by open label use in 17

of the 19 over the remaining 9 months. In the later subgroup 6 MWD, QOL scores, PVR, CI, and NT-proBNP did significantly improve implying some treatment effect.

Beraprost in CTEPH:

29. Nagaya N, Shimizu Y, Satoh T, et al. Oral beraprost sodium improves exercise capacity and ventilatory efficiency in patients with primary or thromboembolic pulmonary hypertension. *Heart* 2002; 87:340-345.
30. Ono F, Nagaya N, Okumura H, et al. Effect of orally active prostacyclin analogue on survival in patients with chronic thromboembolic pulmonary hypertension without major vessel obstruction. *Chest* 2003; 123:1583-1588.
31. Kurzyna M, Florczyk M, Fijalkowska A, et al. Effect of long-term therapy with oral Beraprost on survival of patients with arterial and inoperable thromboembolic pulmonary hypertension. *Pol Arch Med Wewn* 2004; 111(4):477-482.
32. Vizza C, Badagliacca R, Sciomer S, et al. Mid-term efficacy of Beraprost, an oral prostacyclin analog, in the treatment of distal CTEPH: a case control study. *Cardiology* 2006; 106:168-173.

Iloprost in the Treatment of CTEPH:

33. Krug S, Hammerschmidt S, Pankau H, et al. Acutely improved hemodynamics following inhaled iloprost in chronic thromboembolic pulmonary hypertension. *Respiration* 2008; 76:154-159.

In this study of 6 patients on the cath table, significant drops in PVR, mPAP along with increases in CO were seen along with drops in mean systemic arterial pressures and PaO₂. This would imply a potentially reversible vasoconstriction component to the PH seen in CTEPH.

34. Olschewski H, Simoneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347:322-329.

This study of 203 patients with PH, 57 of whom had CTEPH overall showed functional and hemodynamic improvements. However, no formal subgroup analysis of the CTEPH

patients has been offered. Many references in the literature imply, however, that this subgroup did not show significant responses to iloprost by inhalation.

35. **Kramm T, Eberle B, Krummenauer F, et al. Inhaled iloprost in patients with chronic thromboembolic pulmonary hypertension effects before and after pulmonary thromboendarterectomy. Ann Thor Surg 2003; 76:711-718.**

These authors found no significant change in mPAP, PVR of CI before surgery, but did note significant systemic hypotension. Post-op there were significant PVR, mPAP drops and increases in CI in the 10 patients studied.

36. **Figuroa VR, Perez AH, Ferrera NT, et al. Iloprost for chronic thromboembolic pulmonary hypertension. Arch Bronconeumol 2004; 40(7):326-328.**

37. **Kramm T, Eberle B, Guth S, Mayer E. Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy. Eur J Cardiothorac Surg 2005; 28:882-888.**

In this study of 22 patients with persistent PH after PEA, 11 were randomized to inhaled saline and 11 were randomized to iloprost in an attempt to limit pressure stress on fresh sutures, etc. The authors showed significant enhancement of CI with lowering of PVR in the iloprost treated cohort compared to placebo.

38. **Shu HH, Chen JS, Chen YS, et al. Short-term intravenous iloprost for the treatment of reperfusion lung oedema after pulmonary thromboendarterectomy. Thorax 2007; 62:459-461.**
39. **Olschewski H, Ghofrani A, Schmehl et al. Inhaled iloprost to treat severe pulmonary hypertension. Ann Int Med 2000; 132:435-443.**

Trepstinil in the Treatment of CTEPH:

40. **Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous trepstinil sodium therapy in pulmonary hypertension. Chest 2006; 129:1636-1643.**

This study of 99 PAH and 23 CTEPH patients showed ongoing benefit at 3 years in functional class, 6 MWD, and Borg Dyspnea scores for the group as a whole. While subgroup analysis is not offered, the authors state that treatment effects were consistent “across the spectrum of PH”.

41. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Trepostinil for severe inoperable chronic thromboembolic pulmonary hypertension. J Thromb and Haemostas 2007; 5:483-489.

This study enrolled 25 patients over a minimum of 12 months time and compared to a historical control group of 31 “similar” patients from there institution. They found stastically significant improvements in 6 MWD, WHO functional class, BNP levels, and PVR after 19± 6.3 months.

Epoprostenol for CTEPH:

42. Higenbottam T, Butt AY, Westerbeck R, Sharples L. Long term prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. Heart 1998; 80:151-155.

43. Nagaya N, Sasaki N, Ando M, et al. Prostacyclin therapy before pulmonary thrombendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 2003; 123:338-343.

44. Bresser P, Fedullo PF, Auger WR, et al. Continuous intravenous poprostenol for chronic thromboembolic pulmonary hypertension. Eur Resp J 2004; 23:595-600.

45. Tsangaris H, Armaganidis A, Argentos S, et al. Pre-operative long-term optimization with prostanoids in initially inoperable severe chronic thromboembolic pulmonary hypertension (CTEPH): a step forward? J Heart Lung Transplant 2007;26(12):1346-1347.

46. Scelsi L, Ghio S, Campana C, et al. Epoprostenol in chronic thromboembolic pulmonary hypertension with distal lesions. Ital Heart J 2004; 5(8):618-23.

47. Cabrol S, Souza R, Jais X, et al. Intravenous poprostenol in inoperable chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2007; 26:357-362.

This study of 27 consecutive patients found improvements in 6 MWD, mPAP, CI, and TPR along with functional class improvements in most (11/23 at 3 months and 9/18 at 20 months) in those treated with IV poprostenol.

Novel Therapies:

48. Grimminger F, Weimann G, Frey R, et al. First acute hemodynamic study of soluabte guanylate cyclase stimulator riociguat in pulmonary hypertension. Eur Resp J 2009; 33:785-792.

49. Ghofrani A, Hoeper MM, Goeffken G, et al. Riociguat dose titration in patients with chronic thromboembolic pulmonary

hypertension (CTEPH) or pulmonary arterial hypertension (PAH), Am J Resp Crit Care Med [abstract] 2009; A3337.

50. *Leutche HH, Baumgartner RA, Bevec D, et al. Inhalation of vasoactive intestinal peptide in pulmonary hypertension. Eur Resp J 2008; 32:1289-1294.*