8.1. Macitentan for pulmonary hypertension, with thanks to Mitchell Psotka

Pulmonary arterial hypertension (PAH; high pressure in the arteries of the lungs), is a rare, debilitating, and fatal disease. Few medications improve the lives of these patients, and all are expensive. Furthermore, the only medication that decreases mortality is available only intravenously, which is difficult for patients and providers. Pulido et al(Pulido, Adzerikho et al. 2013) reported on a randomized trial of new oral medication, the endothelin receptor antagonist macitentan.

From the abstract:
Methods (abbreviated): We randomly assigned patients with symptomatic pulmonary arterial hypertension to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg. The primary end point was the time from the initiation of treatment to the first occurrence of a composite end point of death, lung transplantation, initiation of treatment with intravenous therapy, or worsening of pulmonary arterial hypertension.

Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
	number of patients (percent)						
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	0.55 (0.32–0.76)	<0.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)				
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)				
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)				
Lung transplantation	0	1 (0.4)	0				
Death due to PAH or hospitalization for PAH as the first event							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25

(a) The authors conclude that "Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension in this event-driven study." Based on the results table above, do you agree?

No. The HR for death from any cause was higher in the 3 mg group. There were no statistically significant differences in mortality. The Cis are very wide.

(b) A pharmaceutical representative comes to your office and tells you that although macitentan is expensive ($7,727 for 30 10 mg tablets[1]), treatment reduced the risk of trial endpoints ("All events related to PAH or death in table above) by 32% so the number needed to treat is not very high. Do you agree? (Note: Only the 10 mg dose of macitentan is available for prescription).

31.4/46.4 = 0.68 RRR = 0.32 46.4% - 31.4% = 15% < 32% NNT = 6.7

(c) Based on your calculations, what is the approximate medication cost to prevent one patient from having an event, assuming 90 weeks of treatment? (The study was 100 weeks, but subjects who died before the end of the study would not incur treatment costs, so 90 weeks of treatment would be a better estimate.)

90 * 7 = 30 * 21 21 * $7,727 = $162,267 per 90-week course of treatment.
NNT*$162,267 = $1,082,138

Pulido, T., I. Adzerikho, R. N. Channick, M. Delcroix, N. Galie, H. A. Ghofrani, P. Jansa, Z. C. Jing, F. O. Le Brun, S. Mehta, C. M. Mittelholzer, L. Perchenet, B. K. Sastry, O. Sitbon, R. Souza, A. Torbicki, X. Zeng, L. J. Rubin, G. Simonneau and S. Investigators (2013). "Macitentan and morbidity and mortality in pulmonary arterial hypertension." N Engl J Med **369**(9): 809-818.

[1] At Target/CVS with coupon on GoodRx 10/25/16