**1025**

**Anticoagulation in Pulmonary Arterial Hypertension: A Decision Analysis**

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**Background:** Pulmonary arterial hypertension (PAH) is a progressive, fatal disease of the pulmonary arteries. Thrombotic pulmonary vascular lesions have frequently been observed during post-mortem examination of PAH patients, and anticoagulation with vitamin K antagonists (VKA) may have benefit in some forms of PAH. Two large studies, the REVEAL and COMPERA registries, evaluated the role of VKA therapy in PAH and reached conflicting conclusions, and as a result the most recent treatment guidelines for PAH offer limited guidance on anticoagulation strategies. Given this uncertainty, we sought to use a decision analytic model to help clarify the expected utility of anticoagulation with VKA therapy in PAH patients across a number of commonly encountered clinical scenarios.

**Methods:** We constructed a 31-state Markov decision analytic model to explore two strategies in PAH patients: anticoagulation with VKA therapy and no anticoagulation with VKA therapy. Patients were able to enter the Markov simulation from 12 different disease states, based on their gender, mode of receiving PAH therapy (via central catheter or not), type of PAH (idiopathic or secondary to connective tissue disease (CTD)), and use of oral contraceptive medication in female patients. Utility was determined from quality-adjusted life years (QALY's), and rates of clinical events were obtained from the literature. Modeled clinical events included thromboembolic complications, mortality, atrial fibrillation, stroke, and bleeding. We used the REVEAL and COMPERA registries to approximate the upper and lower bounds of mortality and VKA therapy clinical effectiveness or harm in the model. Sensitivity analyses were performed on all key assumptions of the model.

**Results:** In the base case analysis, anticoagulation with VKA therapy in idiopathic PAH patients resulted in a gain of 1.6-1.9 QALY's, but a loss of 4.65-5.72 QALY's in those with PAH due to CTD. In IPAH patients the sensitivity of this result was not affected by rates or mortality of thromboembolic complications, bleeding, PAH patient characteristics, or other model assumptions, and anticoagulation would need to improve the yearly mortality rate in idiopathic PAH patients by at least 1% to be the favored strategy. The opposite was seen in patients with PAH from CTD, where anticoagulation resulted in a loss of QALY's, and the yearly mortality rate without anticoagulation would need to exceed 0.75% in order for anticoagulation to become the favored strategy.

**Conclusions:** Anticoagulation is the favored strategy in idiopathic PAH patients, resulting in a gain in QALY's, but causes a loss in QALY's in patients with PAH from CTD. These conclusions were not affected by sensitivity analyses on quality-adjustment factors for health states, rates of transition between health states, or PAH patient characteristics.

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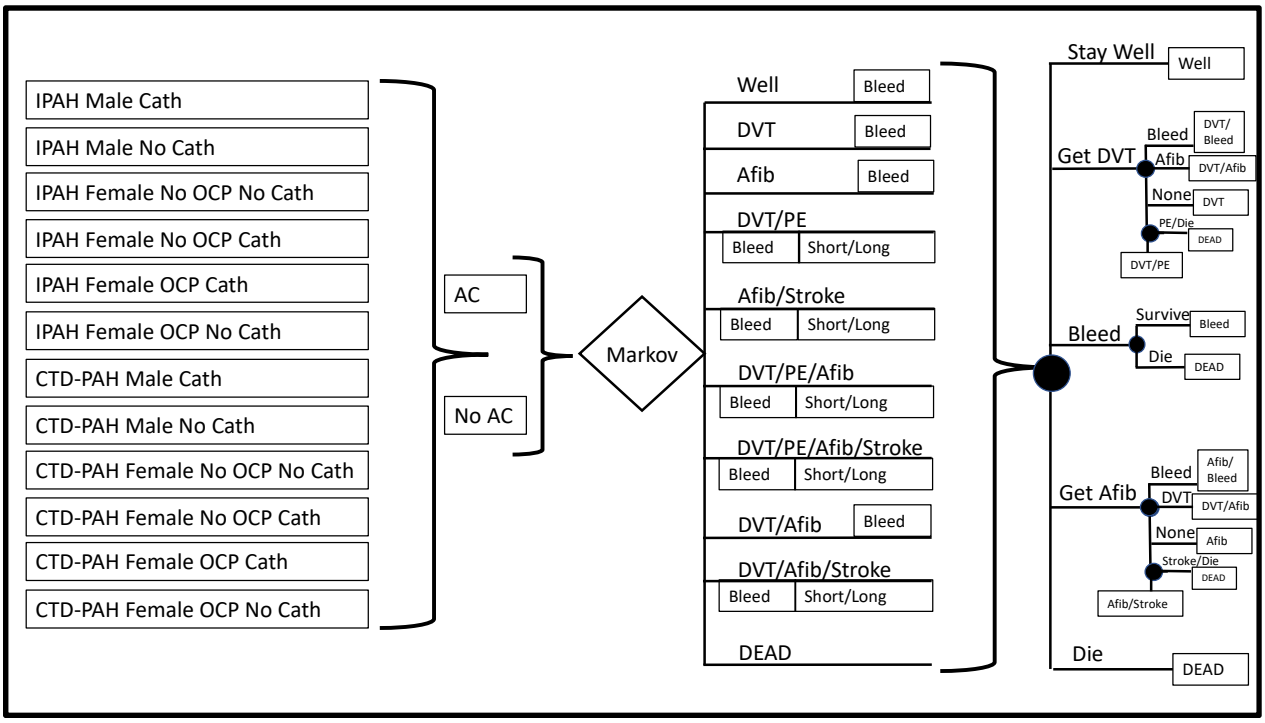
Figure 1. Decision Analytic Model Schematic




Abbreviations: PAH = Pulmonary Arterial Hypertension, IPAH = Idiopathic Pulmonary Arterial Hypertension, CTD = Connective Tissue Disease, OCP = Oral Contraceptive Medications, AC = Anticoagulation (with Vitamin-K Antagonist therapy), PE = Pulmonary Embolism, DVT = Deep Vein Thrombosis, Afib = Atrial Fibrillation

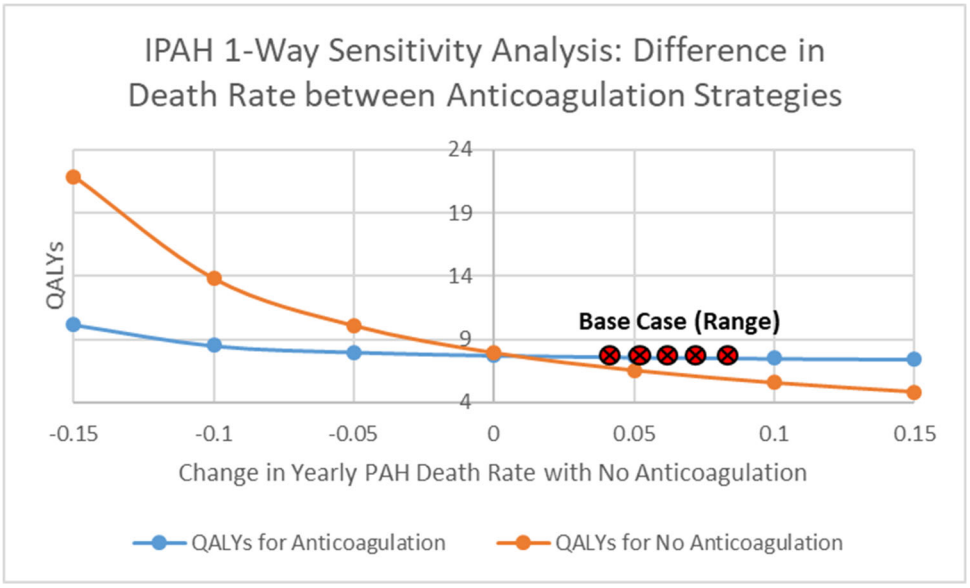
Figure 2. Base Case Analyses of Quality Adjusted Life Years (QALYs)

| | REVEAL Registry Mortality Rates for IPAH and CTD-PAH | | COMPERA Study Mortality Rates for IPAH and CTD-PAH | |
|---|---|---|---|---|
| **Disease State Entering Markov Model** | **Utility AC (QALYs)** | **Utility no AC (QALYs)** | **Utility AC (QALYs)** | **Utility no AC (QALYs)** |
| IPAH Male Cath | 7.53 | 5.94 | 22.93 | 18.60 |
| IPAH Male No Cath | 9.01 | 7.11 | 27.64 | 22.49 |
| IPAH Female No OCP No Cath | 9.02 | 7.12 | 27.72 | 22.58 |
| IPAH Female No OCP Cath | 7.55 | 5.97 | 23.12 | 18.87 |
| IPAH Female OCP Cath | 7.53 | 5.94 | 22.89 | 18.55 |
| IPAH Female OCP No Cath | 9.00 | 7.10 | 27.50 | 22.34 |
| CTD-PAH Male Cath | 4.05 | 8.71 | 8.07 | 10.11 |
| CTD-PAH Male No Cath | 4.85 | 10.53 | 9.66 | 12.19 |
| CTD-PAH Female No OCP No Cath | 4.85 | 10.57 | 9.68 | 12.23 |
| CTD-PAH Female No OCP Cath | 4.06 | 8.78 | 8.09 | 10.17 |
| CTD-PAH Female OCP Cath | 4.05 | 8.69 | 8.06 | 10.09 |
| CTD-PAH Female OCP No Cath | 4.84 | 10.47 | 9.64 | 12.13 |

Abbreviations – IPAH = Idiopathic Pulmonary Arterial Hypertension, CTD-PAH = Connective-Tissue-Disease associated Pulmonary Arterial Hypertension, AC = Anticoagulation with Vitamin-K antagonist therapy (Warfarin), QALY = Quality-Adjusted Life Years, Cath = presence of central catheter, OCP = Use of oral contraceptive medications

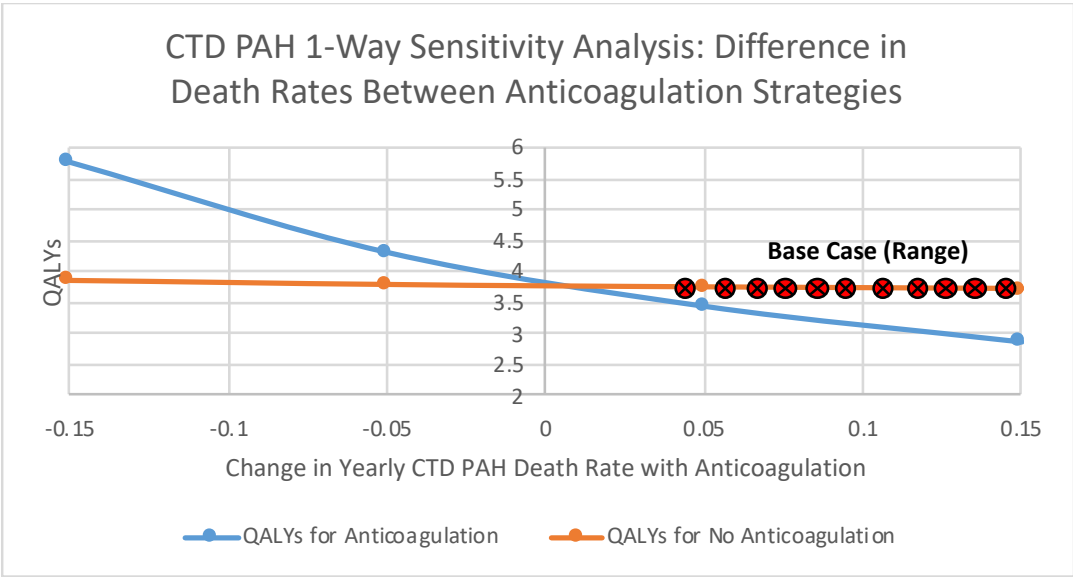
Favored Strategy based on higher Utility

Figure 3. Sensitivity Analysis on Difference in Mortality Rates Between Anticoagulation Strategies in IPAH




Abbreviations – IPAH = Idiopathic Pulmonary Arterial Hypertension

Figure 4. Sensitivity Analysis on Difference in Mortality Rates Between Anticoagulation Strategies in CTD PAH




Abbreviations – CTD-PAH = Connective-Tissue-Disease Associated Pulmonary Arterial Hypertension