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Anticoagulation increases survival in patients with idiopathic pulmonary arterial hypertension

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ABSTRACT   A critical appraisal and clinical application of Olsson KM, Delcroix M, Ghofrani HA, et al. Anticoagulation and survival in pulmonary arterial hypertension: Results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). *Circulation,* 2014;129(1):57-65. doi: 10.1161/CIRCULATIONAHA.113.004526

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Clinical Context

A 66-year-old female presents to the emergency department for new onset shortness of breath, chest pain and leg swelling. She further notes episodes of light-headedness with exertion. She has never lost consciousness during these episodes. These symptoms have been going on for months and are gradually becoming worse. Physical exam reveals a jugular venous distension. Lungs are clear to auscultation. Auscultation of the heart is remarkable for a loud systolic murmur at the left sternal border. In addition, the patient has 1+ pitting edema bilaterally. Chest X-ray reveals cardiomegaly and enlargement of the pulmonary arteries with decreased peripheral vascularity. The ER physician decides to order an ECG. The ECG is remarkable for right ventricular hypertrophy. Labs are remarkable for an elevated brain natriuretic peptide of 155 pg/ml, though not in the range of a heart failure patient. A subsequent echocardiogram shows minimal left cardiac abnormalities, right atrial and ventricular enlargement, and pulmonary hypertension with a systolic pulmonary artery pressure estimated at 65 mmHg.

The patient discloses that she was diagnosed with idiopathic pulmonary arterial hypertension 20 years ago. The doctor has given her medications that dilate the arteries in the lungs. In addition, she is taking warfarin even though she never had a history of venous thrombosis or stroke. She is later discharged and is told to follow up with pulmonology clinic for management of her pulmonary hypertension.

Clinical Question

Does anticoagulation increase survival in patients with pulmonary arterial hypertension?

Research Article

Olsson KM, Delcroix M, Ghofrani HA, et al. Anticoagulation and survival in pulmonary arterial hypertension: Results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). *Circulation,* 2014;129(1):57-65. doi: 10.1161/CIRCULATIONAHA.113.004526

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Related Literature

Literature review began with articles found on UpToDate® and through the Google search engine by combining the keywords "pulmonary arterial hypertension" and "anticoagulation." Pulmonary hypertension is a disease spectrum that is classified as WHO groups I through V according to the Dana Point 2008 Updated Clinical Classification system[1]. This system enables clinicians to categorize a patient with pulmonary hypertension based on underlying etiology, which in turn guides therapy. One subset of pulmonary hypertension is idiopathic pulmonary arterial hypertension (PAH). Interestingly, more providers are recognizing the benefits of using anticoagulants in patients with PAH[2].

The main pathologic changes in PAH are vasoconstriction, vascular smooth-muscle cell and endothelial-cell proliferation, and thrombosis[3]. These findings suggests a disruption in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic factors[4]. Increased thrombi in the pulmonary vasculature will increase pulmonary vascular resistance and lead to right heart strain, ultimately leading to cor pulmonale[5].

Fuster et al. and Bjornsson et al. conducted retrospective studies in which they performed a histological evaluation of lung tissue in female patients diagnosed with PAH. Examination of lung tissue obtained at autopsy revealed that the major histologic feature was thrombi in the pulmonary vasculature, illustrating the importance of a thrombotic mechanism[6,7].

A study by Cohen et al. described a case report in which a 54-year-old man diagnosed with PAH showed resolution of symptoms of dyspnea and fatigue, regression of electrocardiographic signs of right ventricular hypertrophy and regression of elevated pulmonary artery pressure after receiving long-term antithrombotic therapy[8].

Theoretically, giving patients anticoagulants will decrease thrombi formation and it may halt progression of PAH. Examination of the literature revealed that many studies have attempted to evaluate the use of warfarin in PAH patients with mixed outcomes. For example, Roman et al. performed a retrospective case series of 44 idiopathic PAH patients during an eight year interval. The average systolic pulmonary arterial pressure of the cohort was 92 mmHg. The group reported that a combination therapy of warfarin and a calcium channel blocker (diltiazem or nifedipine) helped improve the outcome of 5 patients[9].

In contrast, an archival cohort study by Storstein et al. did not support the use of anticoagulants in patients with idiopathic PAH. The study examined 10 idiopathic PAH patients treated with anticoagulants and seven not treated with anticoagulants over a six year time period. The baseline mean systolic pulmonary artery of the cohort ranged 50-125 mmHg. Patients were treated with anticoagulants, without any other PAH-specific medical therapy. Pathological evaluation of four out of the ten patients who received anticoagulants showed pulmonary artery thrombosis along with arteriopathic changes. Cardiac catheterization was performed in those four patients, and none had exhibited a reduction in their pulmonary artery pressure during treatment. Post-mortem evaluations of the control group revealed high prevalence of vascular thrombotic lesions. Furthermore, the researchers found no difference in survival between the anticoagulant and non-anticoagulant treated patients[10].

Data from observational studies described above suggest that the use of anticoagulation therapy in patients with PAH is still inconclusive. Therefore, a randomized controlled trial is needed to definitively address this important clinical issue. Olsson et al. attempted to address this with the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) study. The COMPERA study is a European pulmonary hypertension registry. The anticoagulation therapies utilized were warfarin (93%), heparins (6%) and novel oral anticoagulants (91%). The purpose of this study was to measure the survival rate of idiopathic PAH and other forms of PAH with and without anticoagulation.

Critical Appraisal

The article by Olsson et al. is a prospective study of 1,283 consecutively enrolled patients in COMPERA registry with newly diagnosed PAH, which falls under a level 1B evidence according to the Oxford Centre for Evidence-Based Medicine. It studied people with pulmonary hypertension between May 2007 and April 2013. From the cohort, 58% received anticoagulation therapy during the trial. The conclusion of the study was that anticoagulation decreases the risk of death in patients with idiopathic PAH. However, anticoagulation increased the risk of death for other forms of pulmonary hypertension. The study also showed that patients with idiopathic PAH who were anticoagulated had a better three-year survival (p=0.006) compared to those that never received

anticoagulation. The survival difference at 3 years remained statistically significant (p=0.017) in a matched-pair analysis of n=336 idiopathic PAH patients. Furthermore, the favorable effects of anticoagulation on survival of idiopathic PAH patients was confirmed by Cox multivariable regression analysis (hazard ratio 0.79, 95% confidence interval 0.66 to 0.94).

This paper had multiple strengths, the first of which is the large sample size, consisting of patients from seven European countries. A large sample size is more representative of the population and will limit the influence of outliers. The use of people from different nations makes the data from this study applicable to a greater percentage of the world population. An additional strength is the prospective design of the study. For example, data collection occurs at regular intervals, thereby minimizing recall bias. The last strength of the study is the low rate of loss to follow up (<3% in all subsets of patients). Prospective cohort studies are especially prone to high dropout rates because they can take a long time to complete. Maintaining a low lost to follow-up rate is critical because patients that leave the study often have a different outcome than those who complete it. With a low rate of loss to follow up, the data is more complete and little bias is introduced. According to Dettori, a good rule of thumb is that <5% loss leads to little bias[12].

Despite these strengths, the study has flaws. First and perhaps most important is that this was not a randomized clinical trial, but a prospective registry. A randomized control trial should have been performed to see if anticoagulation (the intervention) leads to increased survival. In the study, patients who received anticoagulants and those who did not receive anticoagulants were not randomized, and differed in baseline characteristics and PAH medications. Without proper randomization, there is an element of allocation bias. There is a lack of balancing both known and unknown prognostic factors in the assignment of treatment. Importantly, to account for the incompatibility in characteristics between the treatment and no-treatment groups, a matched pair analysis was performed. This analysis requires that every patient that received anticoagulation be compared to a patient with similar baseline characteristics that did not receive anticoagulation. This strategy allows one to assess the effect of the intervention, reducing confounding bias[12].

Another flaw of this study is that the COMPERA database did not have a method to record all bleeding events. Instead, it recorded only serious adverse events, deaths, and causes of death. The major side effect of anticoagulation is increased risk of hemorrhage, especially in the central nervous system and gastrointestinal system[11]. It would have been important to assess if the anticoagulation group had other minor bleeds that did not result in an adverse event. To illustrate: there were a total of 4 cases (2%) during the entire study in which bleeding was found the cause of death. The anticoagulation group experienced 1 of the following: intracerebral bleeding, gastrointestinal bleeding, and hemoptysis. The no anticoagulation group experienced 1 gastrointestinal bleeding event. Therefore, the only thing that can be said is that the bleeding was the cause of death in 2% of the cases and the rate of bleeding was higher in patients who were anticoagulated. In addition, there were 3 non-fatal but serious bleeding events resulting in hospital admission; all occurred in the anticoagulation group (1 subdural hematoma and 2 gastrointestinal bleedings).

The authors did not address the quality of anticoagulation. They state that the target range for the INR was 2-3. However, the authors did not address the percentage of patients that were inside and outside the therapeutic range. If a patient received anticoagulation and s/he was subtherapeutic throughout most of the study, then one would question if the intervention was actually efficacious.

The patient population studied primarily consisted of the elderly. The cohort as a whole had a median age of 68 (Q1=55, Q3=75). For patients receiving anticoagulation, the median age was 70 (Q1=58, Q3=76). For patients not receiving anticoagulation, the median age was 66 (Q1=52, Q3=75). This means that elderly patients diagnosed with idiopathic PAH may not be pure idiopathic PAH. They may have suffered from other forms pulmonary hypertension that were not identified. Examples could be unrecognized parenchymal disease (e.g. subclinical chronic obstructive pulmonary disease or subclinical interstitial lung disease) or unrecognized left heart disease. Classically, idiopathic PAH is found in young to middle-aged females, and it remains questionable whether the data obtained from this study could be applied to this population.

The absolute risk reduction for mortality was 7%. The number needed to treat was 14 patients. This means that 14 patients with idiopathic PAH have to be treated for three years in order to prevent the death of one individual. Fourteen is a relatively low number needed to treat, making anticoagulation a good intervention. The number needed to harm was 14 patients. This means that 14 patients would need to be treated with an anticoagulant for 1 patient to show the harmful effect.

Clinical Application

In the study by Olsson et al., it was concluded that the use of anticoagulants is associated with a better 3-year survival (p=0.006) in patients with idiopathic PAH. However, the data does not support the use of anticoagulation in other forms of pulmonary hypertension. The patient previously described was diagnosed with idiopathic PAH. She is in the appropriate age range of the study and the data from this study supports the use of anticoagulants in patients with her condition.

I learned that it is important for doctors to remind patients that once pulmonary hypertension has been diagnosed, medical therapy is needed. Regular follow-up with a cardiologist or pulmonologist trained in caring for patients with this condition is required. Pulmonary hypertension is a serious illness, and many treatment options are available. For patients with idiopathic PAH, the use of blood thinners is one of those options.

The lessons learned are that (1) anticoagulation is beneficial in patients with idiopathic PAH, which supports current treatment recommendations; (2) The evidence is still indeterminate when it comes to other forms of PAH, and anticoagulation may be harmful in pulmonary hypertension associated with systemic sclerosis; (3) More research is needed in the form a prospective randomized clinical trial to assess the use of anticoagulants in pulmonary hypertension; and (4) the novel oral anticoagulants are well on their way to replacing warfarin as the standard of care for anticoagulation. A study is needed that compares warfarin, heparin injection and novel oral anticoagulants in a head to head trial to determine the ideal treatment for idiopathic PAH.

References

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology*. 2013;62(25):D34-D41. doi: 10.1016/j.jacc.2013.10.029
2. Johnson SR, Mehta S, Granton JT. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. *The European Respiratory Journal*. 2006;28(5):999-1004. doi: 10.1183/09031936.06.00015206
3. Brousseau S, Wang Z, Gupta SK, Meenach SA. Development of aerosol phospholipid microparticles for the treatment of pulmonary hypertension. *AAPS PharmSciTech*, 2017 Jun 05:1-11. doi: 10.1208/s12249-017-0821-2
4. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *New England Journal of Medicine*. 2004;351(16):1655-1665. doi: 10.1056/nejmra035488
5. Schriner RW, Ryu JH, Edwards WD. Microscopic pulmonary tumor embolism causing subacute cor pulmonale: a difficult antemortem diagnosis. *Mayo Clinic Proceedings*, 1991;66(2):143-148. doi: 10.1016/s0025-6196(12)60485-6
6. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation*. 1984;70(4):580-587. doi: 10.1161/01.cir.70.4.580
7. Bjornsson J, Edwards WD. Primary pulmonary hypertension: a histopathologic study of 80 cases. *Mayo Clinic Proceedings*, 1985;60(1):16-25. doi: 10.1016/s0025-6196(12)65277-x
8. Cohen M, Edwards WD, Fuster V. Regression in thromboembolic type of primary pulmonary hypertension during 2½ years of antithrombotic therapy. *Journal of the American College of Cardiology*. 1986;7(1):172-175. doi: 10.1016/s0735-1097(86)80277-7
9. Roman A, Rodes-Cabau J, Lara B, et al. Clinico-hemodynamic study and treatment of 44 patients with primary pulmonary hypertension. *Medicina clinica*. 2002;118(20):761-766. doi: 10.1016/s0025-7753(02)72524-4
10. Storstein O, Efskind L, Müller C, Rokseth R, Sander S. Primary pulmonary hypertension with emphasis on its etiology and treatment. *Journal of Internal Medicine*. 1966;179(2):197-212. doi: 10.1111/j.0954-6820.1966.tb05449.x
11. Dettori JR. Loss to follow-up. *Evidence-Based Spine-Care Journal*. 2011;2(1):7-10. doi: 10.1055/s-0030-1267080
12. Rubin DB. Matching to remove bias in observational studies. *Biometrics*. 1973:159-183. doi: 10.2307/2529684
13. Anderson DW, Kish L, Cornell RG. On stratification, grouping and matching. *Scandinavian Journal of Statistics*. 1980:61-66.
14. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Archives of internal medicine*. 2007;167(13):1414-1419. doi: 10.1001/archinte.167.13.1414