Lessons from the trials

Anticoagulation in pulmonary arterial hypertension: Contemporary data from COMPERA registry

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ABSTRACT

The use of anticoagulant therapy in patients with pulmonary arterial hypertension (PAH) has been controversial for decades. Recommendations for anticoagulation in these patients are often derived from small, retrospective, and single centre studies without any placebo-controlled randomized study. Furthermore, uncertainties exist regarding a number of issues such as patient selection, risk stratification for bleeding, the intensity of anticoagulation, appropriateness of anticoagulation in different types of PAH, and the potential use of new oral anticoagulants.

Recently, the database of the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) has been analyzed to assess the effect of anticoagulation on the long-term outcome of patients with various forms of PAH. This analysis is the largest to date to assess anticoagulant therapy in PAH patients in a prospective design with long observation period. The results of COMPERA lend support to current recommendations for the use of anticoagulant therapy in patients with idiopathic PAH, but not in other forms of PAH. Also, the study confirmed the previously reported concern that anticoagulant therapy may be harmful in patients with scleroderma-associated PAH.

BACKGROUND

The exact role of chronic thrombosis in the pulmonary arteries in patients with pulmonary arterial hypertension (PAH) is controversial. One view suggests that thrombosis is an epiphenomenon related to stasis and endothelial dysfunction. Another view holds that chronic organized thrombotic pulmonary vascular lesions are an integral part of pulmonary vascular remodeling leading to progressive luminal narrowing with increased pulmonary vascular resistance and progression of PAH.[1–2]

Irrespective of whether thrombosis is a cause or consequence of PAH, anticoagulants have been used for decades in PAH patients. The main rationales for the use of anticoagulant therapy in PAH are:

(1) Pathological evidences that thrombi are a common finding in idiopathic PAH patients. In two retrospective studies evaluating histopathology in idiopathic PAH patients (formerly called primary pulmonary hypertension), the prevalence rates for chronic organized pulmonary vascular thromboses were 56% and 57%.[3–4]

(2) Evidence that PAH is associated with prothrombotic abnormalities, causing *in situ* thrombosis. These abnormalities include all components of coagulation cascade: coagulation factors, platelet function, and fibrinolytic system (for a review, see [2]).

(3) Evidence from observational studies that showed better outcomes in idiopathic PAH patients receiving anticoagulant therapy. In a systematic review of seven observational studies, survival benefit was demonstrated in five studies, while two did not support these findings.[5]

However, the use of anticoagulants in patients with PAH has been a controversial subject for decades for several reasons. First, there has been no placebo-controlled randomized trial that has assessed the effectiveness of anticoagulant therapy in patients with PAH. Available data were derived from small, retrospective, and single centre studies. Second, available literature is restricted to idiopathic PAH with almost no published evidence for other types of PAH. Accordingly, the generalizability of survival benefit reported in idiopathic PAH patients to other types of PAH (eg, scleroderma associated PAH) remains controversial. Third, there is lack of data on the added benefit of anticoagulant therapy in patients receiving modern PAH-target therapy. Fourth, little data exist regarding the risk stratification of bleeding in PAH patient receiving anticoagulant therapy.

Currently, the European Society of Cardiology and the European Respiratory Society recommend that anticoagulant treatment should be considered in patients with idiopathic PAH, heritable PAH, and PAH due to use of anorexigens (Class IIa), with a lower level of recommendation in patients with associated PAH (Class IIb).[6] The American College of Chest Physicians clinical guidelines support the use of anticoagulation with a grade "B" recommendation (a moderate recommendation) based on fair level of evidence in idiopathic PAH patients, and weak recommendation based on expert opinion only for other PAH types.[7]

ANTICOAGULATION IN PAH: DATA FROM COMPERA REGISTRY

The database of the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA),[8] was recently analyzed to assess the effect of anticoagulation on the long-term survival in patients with various forms of PAH. COMPERA is an ongoing prospective European pulmonary hypertension registry that began in 2007 with the contribution of 41 pulmonary hypertension centers from 7 European countries.

The study analyzed the data of 1283 patients with newly diagnosed PAH based on right heart catheterization. Patients who received anticoagulation at any time during the registry were grouped into the anticoagulation group ($n = 738$; 58%), whereas patients who never received anti-coagulation were grouped into the no anticoagulation group ($n = 545$; 42%). According to type of PAH, anticoagulation was used in 66% of 800 patients with idiopathic PAH, and in 43% of 483 patients with other forms of PAH. Vitamin K antagonists were used in 93% of patients followed by heparins (6%) and new oral anticoagulants (1%).

In idiopathic PAH patients, during the 3-year follow-up period, the mortality rate in anticoagulation group was 14.2%, versus 21% in the no anticoagulation group (survival advantage, $p = 0.006$). This survival benefit occurred despite the fact that patients in the anticoagulation group had worse baseline hemodynamics. In a matched-pair analysis (based on sex, age, functional class, and pulmonary vascular resistance) the survival difference between both study groups remained statistically significant ($p = 0.017$). Furthermore, multivariable regression analysis confirmed the beneficial effect

of anticoagulation on survival of idiopathic PAH patients (hazard ratio, 0.79; 95% confidence interval, 0.66 – 0.94)

In patients with other forms of PAH, during the 3-year follow-up period, mortality rate in anticoagulation group was 21.9% versus 15% in the no anticoagulation group without statistically significant survival difference ($p = 0.156$).

Among the 208 patients with scleroderma-spectrum of disease associated with PAH, 26.9% of patients in the coagulation group died, compared to 17.3% in the no anticoagulation group without statistically significant survival difference ($p = 0.28$). However, the use of anticoagulants in these patients was associated with a non-significant trend toward a worse survival in the single predictor analysis (HR, 1.82; 95% CI, 0.94 to 3.54; $P = 0.08$)

As regards bleeding risk, the COMPERA database was not designed to systematically capture all bleeding events. Available data denote that, among the 219 deaths, bleeding was attributed as a cause of death in 4 patients (2%). In addition, there were 3 nonfatal but serious bleeding events resulting in hospital admission. Of note, among these 7 bleeding events, 6 occurred in the anticoagulation group.

WHAT HAVE WE LEARNED?

Data of the COPMERA registry lend support to current recommendations for the use of anticoagulant therapy in patients with idiopathic PAH, but not in other forms of PAH. Also, the data substantiated the previously reported concern that anticoagulant therapy may be harmful in patients with scleroderma-associated PAH.

The importance of the COMPERA lies in: (1) being the largest study so far assessing the effects of anticoagulation therapy in patients with PAH; (2) the prospective design; (3) the 3-year observation period; (4) the low number of patients lost to follow-up (< 3%); and (4) the use of modern PAH-targeted therapy including combination therapy in 45% of all patients, reflecting the current real-world practice.

Results of the COMPERA registry open the gate for several unanswered questions related to criteria that should be used to select patients for anticoagulant therapy; risk stratification for bleeding; the optimum target international normalized ratio (INR); the potential role of new oral anticoagulants; and the need for further randomized controlled trials.

Patient selection

The decision of anticoagulant therapy in a patient with PAH should consider the balance between the risk of PAH-related mortality versus the risk of bleeding related to anticoagulant therapy in this particular patient.

Risk of PAH-related mortality

Mortality risk in PAH patients can be assessed by focusing on parameters with established prognostic importance. These prognostic factors can be categorized into clinical risk factors (WHO function class, 6 minutes walk test, clinical evidences of right ventricular failure, and rapid progression of symptoms); echocardiographic risk factors (right ventricular dysfunction, pericardial effusion); hemodynamic parameters (elevated right atrial pressure, low cardiac output index); or laboratory risk factors (elevated NT-pro BNP).[6,9] In this regard, the population of COMPERA are considered to be at intermediate risk for worse outcome (WHO function class III in 75% of patients, mean 6 minutes walk test of 294 m; mean right atrial pressure of 8.8 mmHg and mean cardiac output index of 2.2 L/min/m^2).

Another point to be considered is how early anticoagulant therapy should be initiated in PAH patients. Introduction of anticoagulant therapy at an early stage of the disease may carry the possible advantage of slowing the progression of luminal narrowing in PAH. However, this strategy may be associated with increased life-time exposure to anticoagulant therapy with increased bleeding risk. Alternatively, the use of anticoagulant therapy in patients in an advanced stage of the disease is expected to offer more protection, since these patients have low cardiopulmonary reserve that cannot withstand further arterial obstruction. Nevertheless, these patients may be also at increased bleeding risk related to hepatic and gastrointestinal congestion.

Risk of bleeding

Bleeding in PAH patients is important for two reasons: it occurs in relatively higher rates compared with other diseases; and it may be associated with serious sequelae. In a retrospective single centre study, major bleeding ranged from 2.4 per 100 patient-years for chronic thromboembolic

pulmonary hypertension and 5.4 per 100 patient-years for idiopathic PAH, to 19 per 100 patient-years for PAH associated with connective tissue disease.[10] These rates are considered high compared to the reported rates of major bleeding in patients with atrial fibrillation receiving oral anticoagulants (2.0 per 100 patient-years).[11–12] The occurrence of an otherwise mild bleeding can be a catastrophic event in PAH patients. These patients are volume sensitive and acute blood loss may induce a fatal vicious circle of cardiopulmonary decompensation that leads to irreversible cardiogenic shock. Chronic blood loss will impair cardiopulmonary reserve and in severe anemia both tissue hypoxia and lactic acidosis contribute to increase pulmonary artery pressure.

A number of factors should be considered to assess risk of bleeding in these patients.

1. Type of PAH: bleeding risk is increased in 3 groups of patients with PAH: (a) patients with connective tissue diseases, specially patients with scleroderma in whom the risk of gastrointestinal bleeding is increased due to the presence of luminal telangiectasia[13]; (b) patients with PAH related to congenital heart disease and (c) patients with portopulmonary hypertension with increased risk for gastrointestinal bleeding owing to the presence of varices and abnormal coagulation profile.
2. Comorbidities including chronic kidney disease, chronic liver disease, unexplained anemia, and peptic ulcer.
3. Drug-drug interaction: caution should also be exercised with the concomitant use of PAH-target therapies and warfarin. Bosentan partially induces the cytochrome P450 system, thereby increasing warfarin metabolism and the required dose. The platelet-inhibiting effect of prostacyclin analogues and sildenafil is widely acknowledged, yet its clinical relevance is still unclear, with respect to concomitant use of warfarin.
4. Age: elderly patients are at increased bleeding risk while on anticoagulant. At the same time increased age is associated with increased mortality risk in PAH patients. In the COMPERA,[8] age was an independent predictor of mortality among patients with idiopathic PAH (HR: 1.35; 95% CI: 1.14 to 1.61). Similarly, in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), male patients >60 year was an independent predictor of increased mortality (HR, 2.2; 95% CI, 1.6 to 3.0).[14] Data on the risk-benefit ratio of anticoagulant therapy in pediatric PAH population is lacking.

Unfortunately, the COMPERA database was not designed to systematically capture all bleeding events. All the study could state was that bleeding complications were responsible for $\sim 2\%$ of the deaths in all cohorts, and that serious bleedings occurred predominantly in the anticoagulation group. No data were available regarding less severe bleeding or the development of iron deficiency anemia. Risk factors for increased bleeding were not systematically assessed in COMPERA; the presence of these risk factors might have affected the decision to use (or not to use) anticoagulants, as well as survival.

Target INR
Generally, the target INR in PAH patients varies, from 1.5 – 2.5 in most centers of North America, to 2.0 – 3.0 in European centers.[6] Unfortunately, data regarding INR in the COPMERA study were deficient; it was mentioned that the INR was 2 – 3 in all but one center and that about 58% of patients in the anticoagulation group had received anticoagulants for the entire observation period. Furthermore, COMPERA did not provide data regarding the frequency and duration of INR values inside and outside the target range, or reasons for anticoagulant discontinuation.

New oral anticoagulants
In COMPERA, 6% of patients in the anticoagulant group were receiving new oral anticoagulants. In atrial fibrillation and venous thromboembolism studies, new oral anticoagulants were, on the whole, non-inferior for efficacy and, to different degrees, superior for some bleeding endpoints compared with vitamin K antagonist. However, the use of new oral anticoagulants in PAH patients cannot be recommended because of the lack of evidence on efficacy and safety in addition to the difficulty to reverse the anticoagulant effect in emergency situations and the potential vulnerability to drug-drug interactions with PAH-targeted therapies.

Future research

Given the high mortality in idiopathic PAH and the 20% relative risk reduction in mortality among idiopathic PAH patients in the COMPERA, it would be possibly difficult – from ethical point of view – to have placebo-controlled randomized trial in the future to further assess the efficacy and safety of anticoagulants in idiopathic PAH. Rather, new randomized controlled trials designed for the evaluation of newer PAH drugs should stratify patients according to anticoagulant use. More studies are needed to answer previous questions related to patients' selection and risk stratification, target INR, and role of new oral anticoagulants.

CONCLUSION

Contemporary data from the COMPERA registry support the use of anticoagulant therapy in patients with idiopathic PAH, but not in other types of PAH. Importantly, the data substantiated the previously reported concern that anticoagulant therapy may be harmful in patients with scleroderma-associated PAH. Further research into the role of anticoagulation in PAH is needed to establish best practice recommendations.

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