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REVIEW

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Arterial and venous thromboembolism in chronic obstructive pulmonary disease: from pathogenic mechanisms to prevention and treatment

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Abstract

Chronic obstructive pulmonary disease (COPD) affects approximately 10% of adults older than 40 years and is an important causes of disability and death in elderly subjects. A large proportion of COPD patients suffer from cardiovascular comorbidities. Thromboembolic events contribute considerably to morbidity and mortality in these subjects. This review summarizes the current evidence regarding the association of COPD with increased thromboembolic risk. We discuss multiple mechanisms potentially linking these conditions and available pharmacological interventions reducing the risk of thrombotic arterial and venous events with special attention paid to new oral anticoagulants.

Key words: anticoagulants, COPD, cardiovascular, coagulation, thrombosis

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic disorders in adults. The prevalence of the clinically overt COPD in subjects aged 40 years or more is estimated at about 10% [1]. Furthermore, COPD prevalence is likely to rise because of aging of the Western societies and common exposure to tobacco smoke in the past those currently aged over 50 years.

The disease has substantial burden, evidenced both by direct influence on the affected individuals and socio-economic consequences on societies. In the European Union, COPD accounts for more than a half of health care expenditures on respiratory system diseases [2]. COPD is the third leading cause of death in the United States, and according to the World Health Organization prognosis until 2030, it will become the third leading cause of death also globally [3].

Knowledge on COPD evolved towards growing recognition of a systemic component of the disease and a role of its comorbidities. This is reflected by changes in the Global Initiative for Obstructive Lung Disease (GOLD) definition, which since 2006 has mentioned 'significant extrapulmonary effects' of COPD [4], and recently (since 2011) included the statement that 'comorbidities contribute to overall severity in individual patients' [2]. Cardiovascular diseases (CVDs) are the leading comorbidities in COPD and are responsible for a considerable proportion of hospitalizations and deaths in COPD subjects [4]. CVDs co-existing with COPD include venous thromboembolism (VTE), ischemic heart disease,

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stroke, cardiac arrhythmias and heart failure. Epidemiological data indicate that CVDs occur more commonly in COPD subjects compared to controls without this disease. This association at least partially results from common risk factors, especially tobacco smoking, but there are data suggesting that COPD (or reduced lung function) represents an independent risk factor for CVDs. There is also a growing body of evidence documenting a prothrombotic state in COPD. This review summarizes the current evidence on increased thromboembolic risk in COPD and discusses potential mechanisms behind this link. We also provide data on established and new methods of pharmacological thromboprophylaxis.

COPD and cardiovascular risk: epidemiological data

Data from large clinical trials indicate that CVDs are among the most common causes of death in COPD subjects [5–7]. Observational studies have compellingly shown that diagnosis of COPD increases the risk of CVDs. This association was strongly supported by studies performed in a cohort of the Kaiser Permanente Medical Care Program recipients [8], a combined database from the Atherosclerosis Risk in Communities Study (ARIC), and the Cardiovascular Health Study (CHS) [9]. The Veterans Administration Medical System data demonstrated a significant association of COPD with an increased risk of coronary artery disease, heart failure and atrial fibrillation (AF) [10]. Common risk factors of COPD and CVDs necessitate caution in interpreting the results of observational studies, and indeed not in all of the published studies association of COPD diagnosis with increased CVDs risk was independent [11]. There is also a possibility that not COPD itself, but rather a reduction in lung function is responsible for the increased risk of CVDs. This hypothesis is supported by the studies demonstrating that both obstructive and restrictive patterns of lung function impairment are related to this increased risk [12]. On the other side, also subjects with normal lung function, but with symptoms of chronic bronchitis (chronic cough and sputum production) probably have increased CVDs risk. For example, chronic bronchitis symptoms were associated with increased risk of ischemic heart disease and ischemic heart disease-related death in a 13-year follow-up of a large Finnish cohort [13]. Furthermore, excessive FEV_1 decline, which is a lung function variable related to disease activity in COPD, was also reported to be associated with increased risk of CVDs [14] and ischemic heart disease-related death [15].

Importantly, COPD worsens outcomes in subjects with confirmed ischemic heart disease. Such observations were reported for example in a prospectively followed cohort of patients after percutaneous coronary interventions [16] or in a retrospective study performed in patients after myocardial infarction [17]. In a recently published analysis of a large Swedish registry, COPD was likewise related to increased risk of death after myocardial infarction (crude rates: 24.6% vs. 13.8%, multivariate analysis: HR 1.14, 95% CI: 1.07 to 1.21) [18]. However, this study provided another interesting observation — similarly to other data, association of COPD with increased mortality was attenuated after adjustment for known confounders. The investigators also found that COPD patients less often received effective treatment, including thrombolysis, anticoagulation or β-blockers [18].

Of note, COPD is related to increased risk of AF as evidenced by several observational studies [8, 10]. Long-term follow-up data from large cohorts (Copenhagen Heart Study [19], ARIC Study [20]) have also revealed increased risk of AF in individuals with reduced lung function. Some of the drugs commonly used in COPD (β_2-agonists and theophylline) are known to increase the occurrence of AF. In a large registry of AF subjects, the presence of COPD correlated with worse prognosis (risk of death 26.9% vs. 12.3%; HR 1.49, $p < 0.05$), yet the prevalence of stroke was similar regardless of the lung disease [21]. Recently, COPD has been demonstrated to represent an independent predictor of mortality in a large registry of the European AF subjects [22]. AF in COPD subjects is also recognized as a negative prognostic factor in the context of exacerbations with hypoxia, as suggested in the European Heart Rhythm Association/European Association of Cardio-Thoracic Surgery Guidelines [23]. Association of reduced lung function/COPD with increased risk of stroke was reported in the Copenhagen Heart Study [24] and the British Regional Heart Study [25]. In a study on large series of stroke subjects COPD was identified as an ischemic stroke risk factor [26].

Exacerbations of COPD pose direct threat to patients' life, have negative impact on patients' quality of life and accelerate lung function decline [2]. Thromboembolic events often impact the prognosis during exacerbations of COPD which has been reported to increase the risk of both

myocardial infarction and stroke [27]. Venous thromboembolism (VTE) is also a common threat to hospitalized COPD patients. In a meta-analysis, pulmonary embolism prevalence was estimated to affect 20% of subjects with COPD exacerbation (25% in hospitalized patients, and 3.3% of those treated in the emergency department), whereas deep vein thrombosis was detected in 12.4% of those patients [28]. COPD is associated with increased venous thromboembolic risk as shown in a number of epidemiological studies, including the Kaiser Permanente Medical Care Program data [8] and the General Practice Research Database [29]. VTE in COPD more often manifests as pulmonary embolism with increased risk of death as compared to individuals who do not suffer from COPD [30].

Potential mechanisms

There are several mechanisms that may link COPD with increased risk of thromboembolic complications: 1) systemic inflammation, 2) hypoxemia and enhanced oxidative stress, 3) endothelial dysfunction and 4) a prothrombotic state including platelet hyperreactivity, and augmented thrombin generation, in part associated with inflammatory state [4, 31]. Prolonged low-grade systemic inflammation in COPD is evidenced by increased serum concentrations of inflammatory markers such as C-reactive protein (CRP), fibrinogen, interleukin 6, interleukin 8 and tumor necrosis factor α [32]. Exacerbations, which are important events in the course of COPD, can lead to further elevation in systemic inflammation [33]. Low grade inflammation is a well-known risk factor for coronary heart disease [34] and CRP concentration is associated with increased risk of cardiovascular events and death [35] in COPD. The inflammatory process can influence coagulation in multiple ways. Some indirect evidence comes from *in vitro* studies. CRP may increase plasminogen activator inhibitor 1 activity [36] and decrease tissue plasminogen activator activity [37] and prostacyclin release [38] by endothelial cells. *Ex vivo* studies have identified multiple coagulation abnormalities in COPD. A study done in stable COPD subjects demonstrated higher rates of thrombin generation and formation as well as alterations in multiple plasma coagulation factors [39]. COPD subjects had a prominently elevated level of factor VIII, increased levels of prothrombin, factor V, VII, IX, but reduced concentration of tissue factor pathway inhibitor. Interestingly, these changes were observed irrespectively from the severity of COPD or concentrations of CRP and IL-6 [39]. The presence of circulating active tissue factor (TF) and activated factor XI (FXIa) was detected in a significant proportion (> 10%) of stable COPD patients, indicating ongoing activation of the extrinsic coagulation pathway driven by exposure of TF [40]. In that study, COPD patients with detectable active TF and FXIa had significantly higher CRP, fibrinogen and prothrombin fragment 1 + 2 (F1 + 2) levels, a marker of thrombin generation, which suggests a close link of hypercoagulability with inflammation in this disease. Similar findings were described in patients with coronary artery disease, especially those with acute coronary syndrome [41]. Increased procoagulant activity of TF in COPD was also confirmed in another study [42]. Another abnormality identified in COPD were unfavorable alterations to plasma fibrin clot structure and function, involving the formation of denser networks, more resistant to lysis, as compared to well-matched controls [43]. Interestingly, elevated CRP was a strong and independent predictor of clot parameters in COPD, with improvement of these abnormalities following statin therapy despite negligible effects on CRP concentrations [43]. Similar changes were observed in stable ischemic heart disease [44]. Several studies documented increased plasma concentrations of markers of thrombin formation and/or activity (thrombin-antithrombin III complexes, fibrinopeptide A, F1 + 2) in COPD [45–50]. Of note, hypoxemic challenge caused an increase in thrombin-antithrombin III complexes and F1 + 2 in subjects with COPD [46].

Several investigators have suggested that low-grade inflammation in COPD largely contributes to a prothrombotic state. Inflammation may act through increased platelet activity, as demonstrated by the correlation of CRP and IL-6 concentrations with immature platelet counts in patients with stable ischemic heart disease [47] or with increased platelet derived inflammatory transcripts in the Framingham Heart Study Offspring cohort data [48]. Increased circulating platelet-monocyte aggregates, a well-established marker of platelet activation, were demonstrated in subjects with both stable and exacerbated COPD [49]. It was suggested that low grade inflammation can cause thromboxane dependent platelet activation [50]. In stable COPD patients urinary levels of stable thromboxane metabolite (11-dehydro-TXB_2) were elevated, correlated with partial arterial oxygen pressure and improved after short-term oxygen treatment [51]. β-throm-

boglobulin, a specific marker of platelet activation, was elevated in some, but not all studies in COPD [45, 52], and increased platelet count was associated with increased mortality in patients following COPD exacerbation [53].

Reduced levels of vascular progenitor cells were reported in stable COPD [54] and it was suggested as a potential mechanism of increased CVD risk (via reduced vascular repair capacity) [55].

Systemic inflammation is associated with increased AF prevalence and with decreased chance to restore sinus rhythm [56]. In one randomized trial methylprednisolone treatment significantly decreased the risk of AF recurrence [57]. In the ARIC study, increased levels of factor VIII coagulant activity, fibrinogen and vWf were associated with a higher mortality risk in subjects both with and without AF, while the higher level of protein C — with lower risk of ischemic stroke [58]. Systemic inflammation potentially can also influence the AF risk by affecting cardiac function in COPD subjects [59].

Management of COPD and thromboembolic risk

VTE in hospitalized COPD patients

The risk of VTE in hospitalized COPD patients is increased, inter alia, due to bedrest, advanced age and concomitant diseases. This risk in hospitalized subjects can be assessed with the Padua Prediction Score, a tool validated in acutely ill medical patients (Table 1) [60]. VTE risk in those with "high-risk" score (≥ 4 points) who had not received prophylaxis was estimated at 11%, whereas in those with low risk it was only 0.3%. A study done exclusively in hospitalized COPD patients provided evidence that a history of malignancy and previous episodes of VTE (included in the Padua Score) increase pulmonary embolism risk in this population [61]. A majority of patients hospitalized due to severity of COPD exacerbation will have increased risk of VTE, and also according to the GOLD guidelines they should receive thromboprophylaxis [2]. The ACCP Guidelines advocates low molecular weight heparin, low-dose unfractionated heparin or fondaparinux in these patients [62]. In those with high bleeding risk mechanical prophylaxis, first of all compression stockings, should be used.

Randomized trials addressing the effectiveness of heparin prophylaxis solely in COPD are sparse. A study done in subjects mechanically ventilated due to COPD exacerbation confirmed effectiveness of low molecular weight heparin in reducing VTE risk, yet without documented gain in survival [63]. Evidence indicates that COPD patients should receive thromboprophylaxis like other medical hospitalized patients if their risk of VTE is increased unless there are contraindications e.g. active bleeding.

Table 1. VTE risk assessment using the Padua Risk Score (adapted from [55])

Item	Points/risk
Cancer (metastases and/or chemio- or radiotherapy in the previous 6 months	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Bedrest (with bathroom privileges) for ≥ 3 days	3
Thrombophilia	3
Recent (≤ 1 months) trauma or surgery	2
Age ≥ 70 years	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
BMI ≥ 30 kg/m^2	1
Ongoing hormonal treatment	1
	≥ 4 points suggesting a high risk of VTE

VTE — venous thromboembolism; BMI — body mass index

Unarguably, all hospitalized COPD subjects should be screened for signs and symptoms of deep vein thrombosis/pulmonary embolism. Risk of pulmonary embolism in COPD subjects presenting to emergency department with pulmonary exacerbations was 6.2% in those with clinical suspicion vs. 1.3% in those without. Diagnostic performance of D-dimer as well as spiral computed tomography in the diagnostic work-up of pulmonary embolism is not influenced by COPD exacerbation [64].

There is no data to support thromboprophylaxis in stable COPD subjects outside specific indications. The 2012 ACCP guidelines recommend against routine use of thromboprophylaxis in chronically immobilized patients residing at home, which refers also to subjects with advanced COPD. Despite in the most severe COPD patients additional risk factors such as steroid therapy or respiratory insufficiency may further increase VTE risk, clinical trial assessing low molecular weight heparin in stable, severe COPD subjects on long term oxygen therapy has not demonstrated survival benefit, however it was underpowered

and had low quality [65]. Taken together, decision on thromboprohylaxis at home should be taken on an individual basis.

The decision on the type of prophylaxis used in acutely ill subjects (pharmacotherapy vs. mechanical methods) is mostly based on the bleeding risk assessment. Multiple risk factors of in-hospital bleeding were identified: gastrointestinal ulcer, low platelet count, bleeding history, advanced age (≥ 85 years), hepatic or renal failure, rheumatic disease or cancer) [62]. Of those, active gastroduodenal ulcer, prior bleeding and low platelet count are the strongest predictors of bleeding [66]. Advanced age, which refers to most COPD subjects, also increases bleeding risk while on heparin. Systemic steroid therapy often used in COPD exacerbations is another factor that elevates the risk of gastrointestinal bleeding. The 2012 ACCP guidelines advocate to consider patients to have increased bleeding risk if they have one of the above mentioned factors with strong influence on bleeding risk or multiple risk factors and recommend against routine use of pharmacologic prophylaxis in those subjects. Available means of prophylaxis in patients with high bleeding risk comprise graduated compression stockings or intermittent pneumatic compression.

Oral anticoagulants in COPD

The most common indication for long-term oral anticoagulation in COPD is co-existent AF. Anticoagulation is generally recommended in those with intermediate or high risk of stroke defined as at least 1 point in the CHA_2DS_2-VASc score (Table 2) [67].

COPD subjects with AF (paroxysmal, persistent or permanent) due to frequent other comorbidities and/or advanced age usually fall into the high-risk category. In a large registry of AF subjects, those with COPD significantly more often had CHA_2DS_2-VASc score ≥ 2 (81% vs. 65%) [21]. Both, vitamin K antagonists (VKA) and non-vitamin K oral anticoagulants or novel oral anticoagulants (NOACs) effectively reduce the risk of ischemic stroke and systemic thromboembolism by about 80%, as compared to up to 30% reduction on aspirin alone [68]. The VKA use requires regular laboratory control of anticoagulant effect and thoughtful avoiding of dietary changes and numerous drug interactions, which is often challenging, especially during COPD exacerbations. Multiple drugs, including commonly used antibiotics (macrolides [in particular clarithromycin], tetracyclines, cefuroxime, cefoperazone, fluorochinolones, metronidazole, trimethoprim/sulfamethoxazole) influence VKA metabolism, leading to elevation of INR above 3–4, especially if the therapy lasts more than 5–7 days together with reduced vitamin K intake [69, 70]. Thus, NOACs may constitute a preferred alternative to VKA in these subjects, especially given the current recommendation to choose this option in Europe.

Table 2. CHA_2DS_2-VASc scoring system in the assessment of thromboembolic risk in AF subjects (adapted from [81])

Item	Points
Congestive heart failure/left ventricular dysfunction	1
Hypertension	2
Age ≥ 75 years	2
Diabetes	1
Prior stroke or transient ischemic attack or systemic embolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 64–74 years	1
Female sex	1

0 point — very low risk, 1 point — moderate risk, ≥ 2 points — high risk

NOACs currently available in Europe comprise dabigatran (thrombin inhibitor), apixaban and rivaroxaban (activated FX inhibitors). These drugs were directly compared to VKA in a few large randomized clinical trials in non-valvular AF patients, including the open-label RE-LY Study [71], the ARISTOTLE Study aimed to compare apixaban and warfarin [72] and the ROCKET AF trial [73]. Similar results were published for edoxaban, a NOAC which was approved in Europe in January 2015 [74]. These large clinical trials provided strong evidence for NOACs effectiveness and safety; they are non-inferior to warfarin.

No specific studies compared NOACs with VKA in COPD subjects, yet a significant number of COPD subjects participated in the above mentioned trials [71–74]. This proportion was about 10%, based on the published reports from the ROCKET-AF Trial (11% of all participants) [85] and the ARISTOTLE trial (9% of those with previous stroke or transient ischemic attack) [75]. The European Society of Cardiology guidelines consider NOACs as the preferred option to VKA in non-valvular AF, especially when starting anticoagulation in previously untreated subjects or in those who experienced thromboembolism while on VKA [23]. Switching patients with optimal

anticoagulation on VKA to NOACs is not justified, also in COPD patients free of bleeding tendency.

Potential advantages of NOACs over VKA [76] may be particularly relevant in COPD subjects. NOACs are used in fixed doses without need for monitoring the pharmacological effect and are more convenient when anticoagulation is to be stopped or modified [77]. These situations comprise the need for surgery/invasive procedure. When bleeding risk is high, stopping the drug for ≥ 4 half-life time (usually 2–3 days — Table 3) is recommended before the elective procedure [78]. When assessment of NOACs anticoagulation effect is necessary, routine coagulation tests are less informative than prothrombin time in case of VKA treatment. Factor Xa inhibitors, especially rivaroxaban, do prolong prothrombin time, yet this effect is variable and probably useful clinically only for qualitative assessment of rivaroxaban's effect [78]. APTT provides only imprecise qualitative assessment of dabigatran's effect. Rivaroxaban and apixaban need anti-Xa assay for quantitative assessment. The effect of apixaban can be qualitatively evaluated with modified PT, while dabigatran — with dilute thrombin time or anti-factor II assay. When necessary and feasible, concentration of NOACs can be directly measured in plasma [79, 80].

NOACs differ in pharmacological characteristics (Table 3), which may have important clinical consequences. Impaired renal function may need dose reduction or is a contraindication if chronic disease is in stage 4 or 5 [81]. These factors should be considered when treating COPD subjects, often encumbered with multiple comorbidities.

NOACs generally do not interact with antibiotics, except rifampicin, erythromycin and clarithromycin [81]. Both clarithromycin and erythromycin interact with rivaroxaban and dabigatran, increasing NOAC's effect by approximately 20–50%, while rifampicin decreases the effect of rivaroxaban and increases the one of dabigatran and apixaban [78]. Some other drug interactions of NOACs include amiodarone, verapamil, diltiazem, azole antimycotics, cyclosporine, tacrolimus, HIV protease inhibitors and carbamazepine [82]. Of those interactions with antiarrhythmics, the most important for COPD

Table 3. Pharmacological properties of NOACs (reprinted with permission [76])

	Warfarin	Dabigatran etexilate[a]	Rivaroxaban	Apixaban
Mode of action	↓synthesis of vitamin K-dependent coagulation factors	Direct selective and reversible thrombin inhibitor	Direct selective and reversible activated factor X inhibitor	Direct selective and reversible activated factor X inhibitor
Time to peak plasma concentration	90 min (peak action after 4–5 d)	0.5–2 h	2–4 h	1–4 h
Half-life	36–42 h	12–14 h	5–9 h (young) –13 h (age > 65 years)	8–13 h
Substrate of P-glycoprotein transporter	No	Yes	Yes	Yes
Substrate of CYP enzymes	Yes (CYP3A4, CYP2C9)	No	Yes (CYP3A4/5, CYP2J2)	Yes (CYP3A4, CYP2C9)
Route of elimination	Various[b]	80% renal	66% renal (33% unchanged)	25% renal
Protein binding	99%	35%	90%	90%
Basic daily dose in AF	~5 mg (1–18 mg) target INR 2–3	2 × 150 mg	1 × 20 mg	2 × 5 mg
Reduced daily dose	Not applicable	2 × 110 mg[c]	1 × 15 mg	2 × 2.5 mg
Indications for reduced dosage	Not applicable	— creatinine clearance 30–49 mL/min — HAS-BLED ≥ 3 points — age ≥ 80 years — co-administration of verapamil	— creatinine clearance 30–49 mL/min — HAS-BLED ≥ 3 points	— creatinine ≥ 133 μM — age ≥ 80 years — body weight ≤ 60 kg (2 or 3 criteria MET)

[a]A prodrug that undergoes biotransformation to the active molecule, dabigatran, by esterases; [b]The anticoagulant effect of warfarin is eliminated through synthesis of functionally active coagulation factors rather than through elimination of warfarin; coagulation factor synthesis is hastened by exogenous vitamin K; [c]In the United States: 2 × 75 mg daily (2 × 110 mg not approved)

subjects are verapamil and amiodarone that increase dabigatran's effect and diltiazem that increases apixaban's effect.

Bleeding complications are the major threat for both, patients on anticoagulation and their physicians. Assessment of the bleeding risk with the validated HAS-BLED scale is helpful in managing subjects with AF (Table 4). The risk of bleeding increases with age, which is important as most of COPD subjects are in advanced age [83]. COPD patients often have poor adherence to treatment [84] and those treated with VKA should be supervised thoroughly, as poor control of therapy is another risk factor for bleeding [85]. Most experts consider NOACs as a safer therapeutic option in COPD patients compared with VKA. Large trials comparing NOACs with VKA identified multiple risk factors associated with increased bleeding risk. Of note, in a ROCKET AF trial history of COPD was one of bleeding risk factors [86]. Other risk factors independently associated with major bleeding risk included older age, baseline diastolic blood pressure (DBP) ≥ 90 mm Hg, gastrointestinal bleeding, prior acetylsalicylic acid use, and anemia; female sex and DBP < 90 mm Hg were associated with a decreased risk. Analysis of the ARISTOTLE trial data with apixaban identified older age, prior hemorrhage, prior stroke or transient ischemic attack, diabetes, low creatinine clearance, decreased hematocrit, use of acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs as risk factors for bleeding, COPD was not a risk factor [87]. Subjects with COPD, usually presenting with multiple comorbidities, often have increased bleeding risk.

Table 4. HAS-BLED score to assess bleeding risk in patients with atrial fibrillation (adapted from [81])

Item	Points/risk
Hypertension (systolic pressure > 160 mm Hg)	1
Abnormal renal function	1
Abnormal liver function	1
Age ≥ 65 years	1
Prior stroke	1
Prior bleeding	1
Labile INRs (e.g. time in therapeutic range < 60%)	1
Taking other drugs at the same time (e.g. ASA, NSAIDs)	1
Alcohol intake	1
	≥ 3 points means a high risk of bleeding

INR — international normalized ratio; ASA — acetylsalicylic acid; NSAIDs — nonsteroidal anti-inflammatory drugs

Antiplatelet drugs in COPD

Antiplatelet therapy reduces cardiovascular risk in the prevention and treatment of atherothrombotic events [88]. Indications for antiplatelet therapy are not different in COPD when compared to subjects with normal lung function, yet there are some data, indicating that COPD subjects are less likely to receive proper treatment. A study based on Krakow Registry of Acute Coronary Syndromes data reported that patients with COPD less often received antiplatelet therapy (aspirin and clopidogrel) during hospital stay [89]. Furthermore, they have higher risk of in-hospital death, and multivariate analysis confirmed COPD diagnosis as an independent predictor of in-hospital death. A recently published observational study identified association of aspirin use with improved survival after COPD exacerbation [53] and it was suggested that routine use of low dose aspirin should be considered after COPD exacerbations [90].

Conclusions

A large body of epidemiological data supports hypothesis that COPD increases venous and arterial thromboembolic risk. Diverse coagulation abnormalities were identified in the COPD ranging from those associated with systemic inflammation and hypoxemia to a hypercoagulable state. Further studies are needed to fully elucidate these mechanisms. Unarguably, in every COPD patient emphasis should be placed on thromboprophylaxis when necessary and CVDs should be searched for with implementation of effective pharmacotherapy, once the diagnosis is established. New therapeutic modalities have the opportunity to improve outcomes and possibly prolong patients' lives.

Conflict of interest

The authors declare no conflict of interest.

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