REVIEW SERIES

Multimorbidity, comorbidity, frailty, and venous thromboembolism

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Abstract

Multimorbidity, i.e., the presence of two or more long-term health conditions, is challenging for healthcare systems worldwide. A related term is comorbidity. This denotes any condition that has existed or may occur during the clinical course of a patient who has the index disease under study. Moreover, frailty is also inter-related with multimorbidity but represents a distinct clinical concept. Few studies have explored how multimorbidity and frailty are related to venous thromboembolism (VTE), though many studies have looked at how different comorbidities, especially cancer, affect the outcome of VTE. Recently, a graded association between multimorbidity and VTE has been described. Several multimorbidity disease clusters, such as cardiometabolic and psychiatric disorders, have been associated with VTE. The comorbidity burden, i.e., Charlson Comorbidity Index (CCI), has also been related to short-term mortality after VTE. VTE patients without comorbidities, i.e., CCI = 0, have less than 1% three months mortality. Frailty and CCI have been associated with postoperative risk of VTE. In this review, drivers of multimorbidity and VTE risk, disease networks, and disease trajectories will also be discussed. Further studies including multimorbidity and frailty as predictors for VTE in situations of risk could be of clinical importance. Moreover, it will also be important to determine which diseases should be included in a multimorbidity risk score for VTE.

Introduction

Multimorbidity is a major challenge for healthcare systems worldwide.[1,2] It is defined as the co-existence of two or more chronic or long-term diseases or medical conditions.[1,2] Multimorbidity most often includes non-communicable diseases (NCD), though infectious diseases of long duration may also be included. However, there is no consensus as to which diseases to include.[1,2] Multimorbidity is not only associated with increased mortality, but may also impair quality of life, and increase healthcare requirements and costs.[3] A cross-sectional study from Scotland, UK, showed that 23.2% of 1,751,841 people registered at medical practices in Scotland were affected by multimorbidity.[4] Multimorbidity of NCD is not only a medical issue for high-income countries, but a global burden also affecting low- and middle-income countries.[5] Factors associated with multimorbidity are old age, mental health disorders, female sex, low socioeconomic status, living in socioeconomically-deprived areas, smoking, physical inactivity, and high body mass index.[4,6]

Although multimorbidity is expected to increase with longer lifespans, it is not a new concept.[7] A recent Swedish study has suggested that genetic factors may also contribute to multimorbidity, that it is inherited among twins, siblings, halfsiblings, and cousins, and is correlated with the degree of genetic resemblance.[8,9] In agreement with the Swedish register-based study, genome-wide association studies (GWAS) have shown that many genetic variants are associated with several diseases, which is called pleiotropy.[10,11] Pleiotropy may, therefore, contribute to the inheritance of multimorbidity.[8,9] A study of electronic primary health care records by Amell *et al*. suggested that shared genetic factors among diseases are linked to certain multimorbidities.[12] A study of hospital inpatient data of 385,335 patients in the UK Biobank by Dong *et al*., which also used genetic data, suggested a shared genetic component of multimorbidity.[13] Thus, multimorbidity appears to be a complex trait with both acquired and genetic determinants.[14,15]

Venous thromboembolism (VTE) usually presents as deep-vein thrombosis (DVT) of the leg or as pulmonary embo-

lism (PE).[16] Superficial thrombophlebitis is also a common manifestation, and this is not as harmless as previously believed.[17,18] More rarely, VTE may occur in other veins (cerebral sinus, and veins in the arms, retina, and mesentery).[16] VTE risk factors are acquired or genetic, and are all related to the Virchow triad: stasis of the blood, changes in the vessel wall, and changes in the composition of the blood.[16] Many genetic risk factors involve coagulation abnormalities.[19-21] VTE is a complex trait due to acquired and genetic factors, and might be thought of as a multicausal disease due to multiple gene-gene and gene-environment interactions between risk factors.[16] Typical acquired risk factors are surgery, fracture, hospitalization, infections, exogenous estrogen, and pregnancy.[16,21,22] However, many chronic NCD are also risk factors for VTE, for example, cancer, autoimmune disorders, obesity, heart failure, kidney disease.[21-24] It has recently been suggested that multimorbidity due to the interactions of multiple NCD might be related to a high VTE risk.[25] Several multimorbidity disease clusters, including cardiometabolic and psychiatric disorders, are associated with VTE.[26] Moreover, certain cardiometabolic disorders may even be inherited in the same families with VTE risk.[27] This review will focus on how two or multiple chronic NCD, i.e., multimorbidity, may interact with regard to VTE risk. Different aspects of multimorbidity, and the related concepts of comorbidity and frailty and their relation to VTE, will also be discussed.[28-30]

Multimorbidity, comorbidity, and frailty

Related concepts to multimorbidity are comorbidity and frailty (Table 1).[1,2,28-32] Comorbidity has been defined as any additional ailment co-existing with an index disease.[28,29] In contrast, multimorbidity is defined as ¨the co-existence of two or more chronic conditions, where one is not necessarily more central than the others¨.[29] This distinction might appear trivial, but it reflects the way different parts of the healthcare system handle patients who have multiple chronic conditions (MCC). The concept of multimorbidity is very useful in primary care where the focus may change according to patients' priorities. The concept of comorbidity is often more useful in secondary and tertiary care settings, which have traditionally been structured around diseases or organ systems.[29]

The related condition of frailty is gaining more attention as the population of older adults grows worldwide.[30] Frailty is defined as a decline in functioning across several physiological systems, accompanied by an increased susceptibility to stressors.[30] Despite efforts, no agreement on a standard instrument to identify frailty has yet been achieved.[30] A systematic review has shown that most of the included articles defined multimorbidity as having two or more diseases.[31] Frailty is most often determined according to the Cardiovascular Health Study criteria,[31,32] which define frailty as the presence of at least three of the following: weight loss, low handgrip strength, slow gait speed, exhaustion, and reduced physical activity.[31,32] Different cutoffs were used to define multimorbidity from two to six or more diseases.[31] Instead, several studies used a continuous scale developed on disease count. Alternatively, two indices of multimorbidity were adopted: the Charlson Comorbidity Index (CCI) and the Comorbidity Illness Rating Scale.[31] Using this large number of definitions, multimorbidity prevalence spanned from 2% to 70%.[31] Still, the systematic review showed that frailty and multimorbidity are two related conditions in older adults.[31] Moreover, most frail individuals are also multimorbid, but fewer multimorbid patients present frailty.[31]

Multimorbidity and venous thromboembolism

Few studies have determined the importance of multimorbidity regarding risk of first event of VTE. Using nationwide Swedish registries, Ahren *et al*. studied the association between multimorbidity and VTE in an extended cross-sectional study.[25] Multimorbidity was determined by a counting method using 45 NCD. Multimorbidity was defined by the occurrence of two or more NCD. A multimorbidity score was constructed and defined by 0, 1, 2, 3, 4, 5, or more diseases. Multimorbidity was defined by a score ≥2. The study included 2,694,442 unique individuals. Sixteen percent (N=440,742) of the study population was multimorbid. There was an association between multimorbidity (score ≥2) and VTE, with an adjusted odds ratio (OR) of 3.16 (95% CI: 3.06-3.27) for VTE in individuals with multimorbidity compared with individuals without multimorbidity (score <2). Moreover, there was a graded association between the number of diseases and VTE. The adjusted OR was 1.94 (95% CI: 1.86-2.02) for one disease (i.e., no multimorbidity), 2.93 (95% CI: 2.80-3.08) for 2 diseases, 4.07 (95% CI: 3.85-4.31) for 3 diseases, 5.46 (95% CI: 5.10-5.85) for 4 diseases, and

Table 1. Definitions of multimorbidity, comorbidity, and frailty. [1,2,28-32]

Concepts	Definitions
Multimorbidity	Presence of 2 or more long-term health conditions
Comorbidity	Any additional co-existing disorder to an index disease
Frailty	A decline in functioning across several physiological systems, accompanied by an increased susceptibility to stressors

9.08 (95% CI: 8.56-9.64) for ≥5 diseases.[25]

Using principal component analysis (PCA), nine multimorbidity disease clusters were identified: F1-F9.[8,9,26] OR for VTE were calculated for each of the nine. Forty-four of the individual 45 NCD were associated with VTE.[26] Seven of these multimorbidity clusters were associated with VTE. The adjusted OR for VTE in the multimorbid patients for the first three clusters was: F1 (cardiometabolic diseases) 3.44 (95% CI: 3.24-3.65), F2 (psychiatric disorders) 2.25 (95% CI: 2.14-2.37), and F3 (digestive system diseases) 4.35 (95% CI: 3.63-5.22). There was an association between multimorbidity severity and OR for VTE. For example, the occurrence of at least five diseases in F1 and F2 was associated with OR for VTE of 8.17 (95% CI: 6.32-10.55) and 6.31 (95% CI: 4.34-9.17), respectively.[26] Most interestingly, in a Swedish family study, VTE density in pedigrees was significantly associated with obesity, diabetes, gout, varicose veins, and arterial embolism and thrombosis (excluding stroke and ischemic heart disease) in the offspring.[27] This shared familial susceptibility between VTE and these cardiometabolic disorders may be due to biological (genetic) or acquired (shared familial environment) factors.[27]

In a cross-sectional analysis of women in the Genes & Health British-South Asian cohort (N=20,048), 439 participants had a VTE event (2.2%).[33] VTE prevalence increased with obesity, hypertension, dyslipidemia, chronic kidney disease, estrogen use, and in the presence of Factor V Leiden. Presentation of one of the above medical conditions was independently associated with VTE with an OR of 1.6 (95% CI: 1.2-2.0); 2 medical conditions: OR 2.7 (95% CI: 2.0-3.7); 3 medical conditions: OR 5.3 (95% CI: 3.8-7.4); 4 medical conditions: OR 8.1 (95% CI: 4.9-13.0).[33]

So far, no longitudinal or follow-up cohort study has been published regarding multimorbidity and VTE risk. Bidirectional association between different diseases in the multimorbidity definitions used and VTE may be a potential problem. However, increasing multimorbidity exhibits a strong association with VTE.[25,26]

Comorbidity and venous thromboembolism

Venous thromboembolism (VTE) is often accompanied by co-morbidities (Table 2).[34-38] Comorbidities from two Swedish studies, the PREFER study, a study of hospitalized patients in the United States, and one Danish study are presented in Table 2.[34-38] The selected comorbidities were not identical and the exact numbers varied depending on the study population (Table 2).[34-38] The PREFER study, performed across seven European countries, followed 3,455 patients with acute VTE over 12 months. Only 13% and 16% of the PE and DVT patients had no co-morbidities. Twenty-four percent of PE patients and 22% of DVT had three or more co-morbid conditions in the PREFER study.[34] PE and DVT patients without comorbidities had a 12-month mortality rate of 1.8% and 1.7%, respectively. The most common comorbidities were cancer, liver disease, lower extremity paralysis, respiratory disease, renal disease, cardiovascular risks, bone and joint disease, cardiovascular comorbidity, and venous disease.[34] In the PREFER VTE registry, frequency and severity of co-morbidities increased mortality rates up to 30%.[34] The EQ-5D-5L index (health-related quality of life [HrQoL]) in patients without co-morbidities was 0.826 and 0.838 for PE and DVT, respectively.[34] These scores decreased to 0.638 and 0.555 in the presence of co-morbidities. Thus, co-morbidities in VTE patients are common, and have an impact on mortality and HrQoL. The authors, therefore, suggest that awareness of the presence of co-morbidities needs to be taken into consideration when making VTE-related treatment decisions.[34]

Among comorbidities, cancer[34] is well-established as an important comorbidity.[34,35] In a Swedish nationwide study, cancer was the strongest predictor for mortality (HR: 8.11; 95% CI: 7.812-8.42).[35] Several other comorbidities were also associated with increased mortality after first VTE event: heart failure (hazard ratio [HR]:1.695; 95% CI: 1.584-1.815), peripheral vascular disease (HR: 1.249; 95% CI: 1.158-1.346), coronary heart disease (HR: 1.171, 95% CI: 1.106-1.24), cerebrovascular disease (HR: 1.495, 95% CI: 1.411-1.584), diabetes mellitus (HR: 1.491; 95% CI: 1.41-1.577), psychiatric disease (HR: 1.468; 95% CI: 1.404-1.535), other pulmonary disease (HR: 1.504; 95% CI: 1.403-1.611), and liver disease (HR: 2.197; 95% CI: 1.956-2.468).[35] However, this study did not assess the influence of the occurrence of multiple comorbidities.[35] A Swedish study of short-term mortality (i.e., first three months) among 41,700 Swedish born patients with a first-time VTE (July 2005-August 2012) found that CCI was a strong risk factor for mortality (CCI = 1 [HR: 2.93; 95% CI: 2.32-3.72], CCI = 2 [HR: 8.65; 95% CI: 7.16-10.46], CCI = 3 [HR: 22.25; 95% CI: 18.73-26.44] compared with CCI = 0).[39] The mortality rate was only 0.70% in patients with CCI = 0. In receiver operating characteristic (ROC) analysis, the area under the ROC curve for CCI was 0.84 (0.83-0.95).[39] Thus, CCI is a strong predictor for short-term mortality in VTE and co-morbidities are important for risk assessment of VTE.

An interesting observation in the two Swedish studies prognostic study of mortality after VTE was that patients with family history of VTE had significantly fewer comorbidities than those without family history of VTE.[35,39] According to the multicausal disease theory for VTE this suggests that comorbidities are an important risk factor for VTE.[16] If a patient is genetically predisposed for VTE, fewer triggers and comorbidities are needed to provoke a VTE event.[16,35,39] In contrast, augmented CCI (aCCI) was only a weak risk factor for postoperative VTE after joint replacement;[40] HR for aCCI = 2 was 1.21 (95% CI: 1.01-1.45). However, aCCI was still a strong risk factor for postoperative bleeding after joint replacement with an HR of 2.30 (95% CI: 2.02-2.62) for aCCI = 2.34.[40] Therefore, the usefulness of a comor-

Table 2. Comorbidities among patients with venous thromboembolism in 2 Swedish nationwide studies, the PREFER study, a study of hospitalized patients in the United States, and one Danish study.[34-38]

Co-morbidity	VTE Swedish[35]	VTE Swedish[36]	PE PREFER[34]	DVT PREFER[34]	VTE US[37]	VTE Danish[38]
	Prevalence (%)					
No co-morbidity	ND	ND	13	16	ND	ND
>1 co-morbidity	ND	ND	87	84	ND	ND
1 co-morbidity	ND	ND	21	23	ND	ND
3 co-morbidities	ND	ND	24	22	ND	ND
5 co-morbidities	ND	ND	3	2	ND	ND
Anemia***	ND	ND	ND	ND	26.8	ND
Arthritis	ND	4.0******	ND	ND	3.4	4.0
Atrial fibrillation	4.9	10.9	ND	ND	ND	ND
Bone and joint disease	ND	ND	15	19	ND	ND
Cancer	20.8	20.3	17	16	13.7**	18,2
Cardiovascular comorbidity	ND	ND	67	60	ND	ND
Cerebrovascular disease	6.2	4.4	ND	ND	ND	8.2
Coronary heart disease	7.6	14.6	ND	ND	ND	3.4#
CV risks	ND	ND	57	46	ND	ND
Dementia	ND	ND	ND	ND	ND	1.9
Diabetes	7.2	ND	ND	ND	23.9	9.2
Heart failure	4.1	14.4	ND	ND	12.8	5.0
Hypertension	14.4	ND	ND	ND	53.9	ND
Hypothyroidism	ND	ND	ND	ND	11.1	ND
Inflammatory bowel disease	2.3	2.2	ND	ND	ND	ND
Liver disease	1.2	1.0	3	3	2.4	1.6
Lower extremity paralysis	ND	ND	1	1	4.1	0.3
Obesity	2.1	ND	ND	ND	12.2	ND
Peripheral vascular disease	3.6	ND	ND	ND	6.1	5.2
Psychiatric disease	14.0	7.4****	ND	ND	20.2*	ND
Pulmonary disease	7.5	5.6*****	10	7	21.1	11
Renal disease	ND	3.3	6	6	15	2.6
Varicose veins	2.8	ND	ND	ND	ND	ND
Valvular disease	ND	ND	ND	ND	4.4	ND
Venous disease	ND	ND	33	39	ND	ND

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep venous thrombosis; ND: not determined; CV risks: the presence of cardiovascular (CV) risk factors hypertension, dyslipidemia, and diabetes. *Depression, alcohol abuse, drug abuse, and psychosis. **Metastatic, solid, and lymphoma. ***Deficiency or blood loss. ****Depression, psychosis and alcohol abuse. *****Chronic obstructive pulmonary disease. ******Systemic connective tissue disorders. #Myocardial infarction.

bidity index such as aCCI in predicting postoperative VTE remains to be proven.

Frailty and venous thromboembolism

Few studies have determined the importance of frailty indices to determine risk of postoperative VTE.[41-43] Frailty appears to be associated with both postoperative morbidity and mortality and VTE after colorectal surgery.[41-43] Another study also found an association between frailty and VTE risk following hip fracture surgery.[44] Thus, frailty appears to be an important research topic regarding postoperative VTE risk. However, it remains to be determined to what extent postoperative risk associated with frailty is independent of comorbidities.

Folsom *et al*. studied frailty in a community setting and found an association between frailty and incidence of idiopathic VTE.[45] Thus, frailty may be an important factor to take into account generally in prediction models for VTE.

However, it is not yet known if frailty is an independent risk factor for VTE with regards to multimorbidity, although frailty is common among VTE patients and many VTE patients may benefit from additional efforts to improve physical functioning.[46]

Disease networks and disease trajectories

In addition to multimorbidity, disease networks look beyond combinations or pairs of disease.[12,47] With the growing complexity of multimorbidity, there is a need to examine disease associations at the population level, in both chronic and acute conditions, and to study disease trajectories and progression patterns.[48] Siggaard *et al*. have created the Danish Disease Trajectory Browser (DTB) that explores 25 years of data from the Danish National Patient Register.[48] The dataset is made up of 7.2 million patients and 122 million hospital admissions. Users may identify statistically significant diagnosis pairs and combine them to linear disease trajectories.[48] It is based on the International Classification of Diseases (10th revision; ICD-10). *Online Supplementary Figure S1* shows it is also possible to study disease networks, for example, for pulmonary embolism (ICD-10 code: I26);[48] mortality is also included, using data from the Danish Register for Causes of Death. The importance of cancer for development of pulmonary embolism can easily be seen in *Online Supplementary Figure S1*, but also cardiometabolic disorders, autoimmune diseases, and respiratory disorders.[48] Trajectories to death are also visualized, for example, via cardiac arrest.[48]

Drivers of multimorbidity and venous thromboembolism risk

Accelerated aging appears to be linked to many of the most common chronic disorders such as coronary heart disease (CHD), osteoarthritis, osteoporosis, type 2 diabetes (T2D), metabolic syndrome, chronic renal disease (CKD), Alzheimer disease, chronic obstructive pulmonary disease (COPD), and interstitial lung disease.[49] VTE is also an age-dependent disease, and old age is a strong risk factor for both multimorbidity and VTE.[4,16] A number of common mechanisms for many common age-dependent diseases have been suggested, including telomere shortening due to cellular senescence with DNA damage, activation of PI3K-AKT-mTOR signaling, defective autophagy, impaired mitochondrial function, stem cell depletion, epigenetic changes, abnormal microRNA patterns, immunosenescence, and chronic low-grade inflammation (known as "inflammaging").[49] Several of these pathways are driven by chronic oxidative stress with reduction of anti-aging molecules, such as sirtuins and Klotho.[49] Figure 1 shows how accelerated aging is linked to multimorbidity and VTE. For example, inflammation is recognized as being a direct driver for VTE, and some consequences of accelerated driving may thus directly increase VTE incidence.[20,23,24,50] The understandings of these molecular mechanisms have suggested novel therapeutic targets and drugs that might slow the aging process, but lifestyle interventions, such as changes in diet and increasing physical activity, can also contribute.[49] In the future, novel treatments may target the common pathways involved in multimorbidity, and this will be an important research area.[49] Broader access to data opportunities across modalities and disciplines could catalyze research into multimorbidity.[51] Multimorbidity should be given greater consideration in drug development, trial design, and development of clinical guidelines.[51]

Discussion

Multimorbidity, comorbidity, and frailty are inter-related concepts that have been rather neglected as far as their implications for VTE risk and treatments are concerned.[1,2,28-32] Thus, the literature on the importance of the impact of multiple diseases on VTE risk is limited. It appears that there is a strong association between severity of multimorbidity, i.e., number of diseases, and VTE.[25,26] Better understanding of multimorbidity mechanisms[49,51] and prevention of multimorbidity may also lead to a decrease in the incidence of VTE. The importance of multimorbidity for VTE prediction and prophylactic treatment remains to be determined, as does the presence of multiple comorbidities among VTE patients and risk of recurrence. There is no current consensus as to which diseases to include under 'multimorbidity'. Different multimorbidity combinations could have different impacts on the associated VTE risk. Thus, it will be important to test which diseases should be included in the definition of multimorbidity regarding VTE risk. Identification of specific and common disease clusters may be of benefit.[26] For example, a systematic review found that the two most important and recognized multimorbidity disease clusters are cardiometabolic disorders and psychiatric disorders.[52] These two disease clusters are also associated with VTE.[26] There are several different methods to study disease clustering, but there is no consensus as to which to use.[53] It will be important to carry out follow-up studies to determine whether multimorbidity is associated with incidence of VTE in general and in situations of VTE risk.

As there might be a genetic cause of multimorbidity,[8,9,13] it will also be important to determine the genomic cause of multimorbidity and whether it will be possible to construct a genetic risk score that could predict, not only multimorbidity, but also VTE. The availability of GWAS, whole exome and whole genome sequencing data, and a large number of phenotypic variables in the UK Biobank will make this possible in a large study population.[54] Disease networks should also be studied to understand the cause of multimorbidity and its genetics.[55,56]

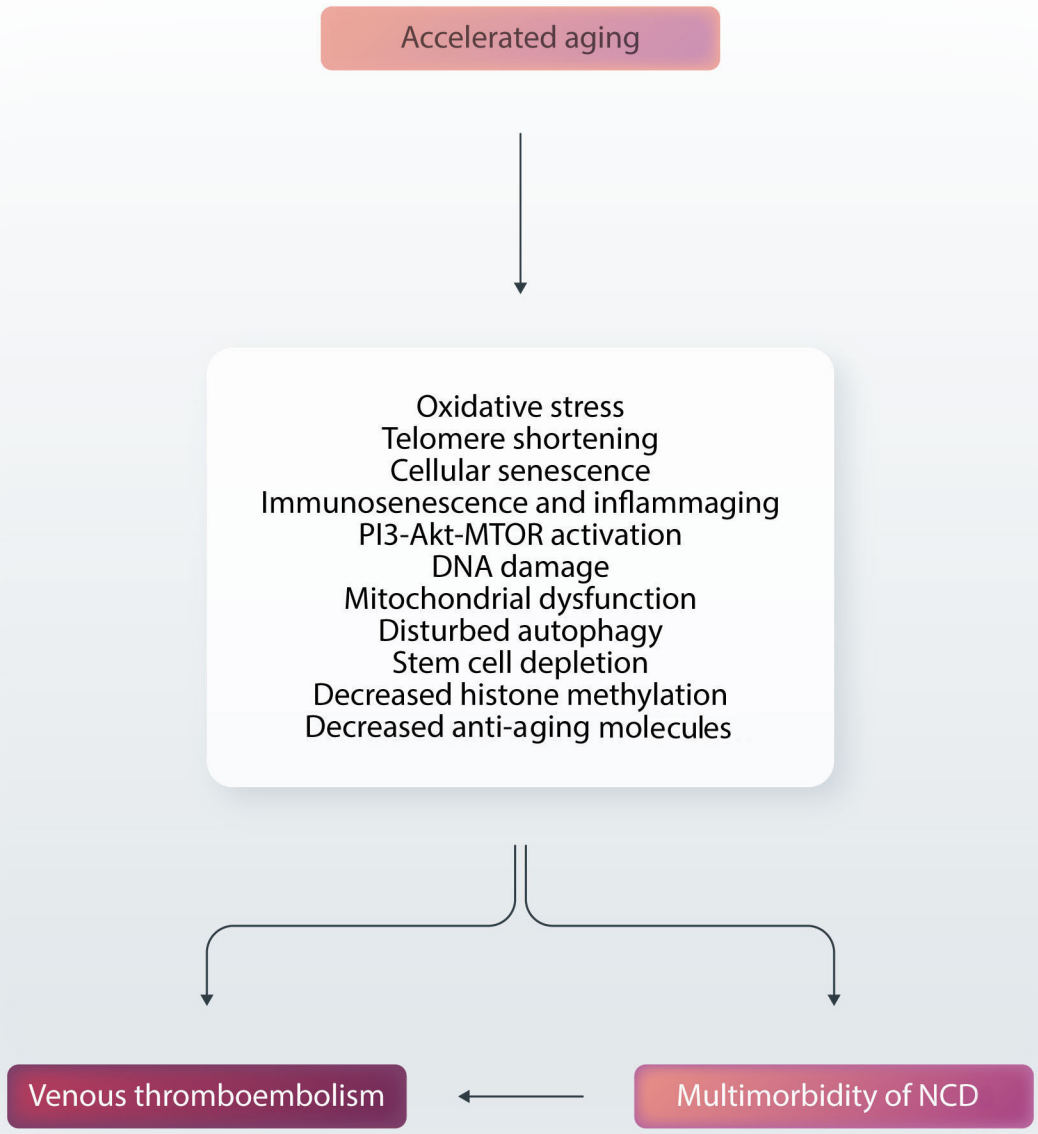

Figure 1. Accelerated aging-related non-communicable disease. Many chronic non-communicable diseases (NCD) are associated with accelerated aging. Common mechanisms of accelerated aging[49] are shared between these diseases and these mechanisms may lead to multimorbidity that increase the risk of venous thromboembolism (VTE). However, some mechanisms of accelerated aging, for example, inflammation may also directly affect risk of VTE. PI3K: phosphoinositide-3-kinase; mTOR: mammalian target of rapamycin.

Clinical implications

Multimorbidity, comorbidity, and frailty are common among VTE patients and have been neglected research topics. It is likely that the identification of useful multimorbidity scores to include in risk prediction models in different clinical scenarios will increase accuracy. Comorbidity scores might also be of use to estimate prognosis in patients with VTE. For example, regarding short-term mortality, a CCI = 0 is associated with a good prognosis and only 0.70% mortality.[39] In the future, novel treatments may target the common pathways involved in multimorbidity, which may also lead to better prevention of VTE.

Conclusions

In conclusion, multimorbidity is a common condition that is associated with VTE. It is likely that risk prediction accounting for multimorbidity in the models used will be more accurate. However, more research is needed to identify the most suitable conditions to include in multimorbidity scores for VTE prediction. Moreover, research on multimorbidity disease mechanisms may also lead to novel and improved ways to prevent VTE.

Disclosures

No conflicts of interest to disclose.

Contributions

BZ drafted the manuscript. JMC critically revised the manuscript.

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