In biology, thrombosis is a mechanism of maintaining the integrity of biological surfaces in higher mammals, limiting fluid loss, and facilitating the recognition, containment, and destruction of pathogens and foreign materials by a scaffold of fibrin and DNA strands. However, thrombosis may also lead to vascular occlusion and subsequent tissue damage.

In medicine, thrombosis is a hallmark of life-threatening cardiovascular diseases, such as myocardial infarction, stroke, or venous thromboembolism representing major causes of death in the Western civilization. Every year 17 million individuals die from cardiovascular disease (1, 2), comprising almost half of the global death toll in Europe. For example, in Austria, 34,000 patients suffered a cardiovascular death in 2012, accounting for 42.7% of all deaths, which is 1.7-fold the death toll of malignant diseases (3).

Cardiovascular science beyond clinical observation and anatomical dissection emerged in the late 19th and early 20th centuries. A key observation was the epidemiological connection of hypertension and elevated plasma lipids with atherosclerotic vascular disease (4). Based on a more profound understanding of these risk factors, including exercise, body weight, and glucose metabolism, preventive measures were tested, leading to both primary and secondary prevention programs that have become powerful modulators of disease decreasing events by almost half. Since then, the establishment of coronary care units, cardiac catheterization, angioplasty, and surgery and the advent of modern medications many of which interfere with thrombosis and platelet aggregation, have contributed to fundamental improvements in cardiovascular care. However, much of the advances in cardiovascular science have been in the thrombosis field, stimulated by the discovery that myocardial infarction was due to thrombi in the coronary arteries (5). Traditionally, thrombosis has been viewed as the biochemical result of regulated cascades of protein interactions characterized by the activation of factor X and the activation of thrombin, resulting in the formation of fibrin. Accordingly, treatments for myocardial infarction, stroke, and venous thromboembolism have targeted pathways or more recently, individual protein moieties (Figure 1). Table 1 summarizes landmark trials leading to the approval of individual compounds. Over 50 years, a plethora of treatments has been brought to market (Table 1), with high efficacy and safety profiles that have contributed to the observation that death rates per 100,000 population were decreased from 450 in the 1950s to 150 around 2010 (6). For example, while 20–30% of hospitalized patients with myocardial infarction died within 30 days due to their underlying disease, this number has been substantially decreased to <5% most recently (7).

The public domain is thrilled with advances of cardiovascular medicine, and needs for deeper insights are hardly convincing in an environment of harmonized health care providing infarction networks, stent-for-life programs, and generally high standard guidelines in cardiovascular care. However, do we understand thrombosis, do we understand recurrence, or do we prefer, for example, to mandate life-long factor X inhibition (38, 46–48) and statins (49) in patients at risk, without further investigation of underlying mechanisms?

More recently, a new view of thrombosis has emerged accounting for thrombosis as a vascular disease involving the dynamic interaction between platelets, circulating inflammatory cells, nucleic acids and proteins, and resident cells of the vascular wall. Milestones along the way of integrating the vessel wall in the thrombotic process were the discovery and action of nitric oxide (50, 51), the delineation of the LDL-cholesterol pathway (52, 53), the role of soluble and membrane bound tissue factor in atherosclerosis (54), and most recently the concept of “immunothrombosis” (55), linking inflammation and thrombosis as regulators of vascular integrity. Consequently, it was understood that the hemostatic system is a modulator of atherosclerosis (56). Thrombosis comprises both acute clotting and the more time-consuming process of thrombus resolution, which represents a vascular remodeling process that is driven by inflammation, angiogenesis, and cells of the innate immune system. A stimulus leading to thrombus formation induces an innate immune response that is supported by neutrophils, lymphocytes, macrophages, by specific thrombosis-related molecules, and neutrophil extracellular traps (NETs), underpinning the importance of the following questions:

Is thrombosis the underlying process behind both arterial and venous disease that oftentimes combines in individual patients? (57) Do we understand endothelial dysfunction, and is it the nidus for thrombosis, and eventually vascular occlusion? And why do acute pulmonary emboli transform into chronic vascular obstructions in chronic thromboembolic pulmonary hypertension? Do...
Table 1 | Overview of treatments approved for vascular thrombosis (antithrombotics, comprising thrombolytics, anticoagulants, and antiplatelet drugs).

| Concept                      | Mechanism of action | Compound (key reference) | Indication                                                                 | Benefits/Harms                                                                 |
|------------------------------|---------------------|--------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Antiplatelet drugs           | COX inhibition      | Acetylsalicylic acid/Aspirin (8) | Prevention of cardiovascular events                                         | Increased risk of bleeding when combined with NSAIDs                           |
|                              | ADP receptor/ P2Y_{12} inhibition | Clopidogrel (9) | Prevention of thrombotic events                                             | Pro-drug limited by metabolism, irreversible                                  |
|                              |                     | Clopidogrel (10)        | ACS                                                                        | Pro-drug limited by metabolism, irreversible                                  |
|                              |                     | Prasugrel (11, 12)      | Prevention of thrombotic events                                             | Rapid onset of action, high efficacy, particularly in diabetic subjects,      |
|                              |                     |                          |                                                                            | increased bleeding rates in those aged >75 years, and in those with previous  |
|                              |                     |                          |                                                                            | stroke and a weight less than 60 kg, irreversible                             |
|                              |                     | Ticagrelor (13)         | Prevention of thrombotic events particularly in STE-ACS                    | Rapid onset of action, reversible, high efficacy, low bleeding rates, provides |
|                              |                     |                          |                                                                            | a survival benefit in ACS                                                     |
| Phosphodiesterase inhibition | Cilostazol (14)     |                          | Reduction of symptoms of intermittent claudication                        | Phosphodiesterase 3 inhibitor, potentially dangerous in severe heart failure  |
| Glycoprotein IIb/IIIa inhibition | Abciximab (15, 16) |                          | For use in individuals undergoing PCI with or without stent placement to decrease the incidence of ischemic complications due to the procedure | Effective prevention of ischemic events, particularly in diabetic subjects, and subjects with chronic kidney disease, increased bleeding rates only in high-risk patients |

(Continued)
| Concept             | Mechanism of action | Compound (key reference) | Indication                                                                                          | Benefits/Harms                                                                                      |
|---------------------|---------------------|--------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Tirofiban (17)      |                     |                          | Reduction of the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with NSTE-ACS | Rapid onset and short duration of action (4–8 h)                                                   |
| Eptifibatide (18)   |                     |                          | Reduction of the risk of acute cardiac ischemic events (death and/or myocardial infarction) in patients with UA or NSTE-ACS both in patients who are to receive medical treatment and those undergoing PCI | Short half-life                                                                                     |
| Anticoagulants      | Vitamin K antagonism| Vitamin K antagonists (19)| Prevention and treatment of venous thromboembolism, atrial fibrillation, mechanical and bioprosthetic heart valves, post-myocardial infarction, recurrent systemic embolism and other indications | Accepted standard, reproducible results, high exposure rates, cheap, no contraindication in patients with GFR <30 mL/min |
| Factor Xa inhibition| Unfractionated heparin (20–23) new ESC Guidelines pending 2014 | Low-molecular weight heparins, e.g., enoxaparin (23, 24) | Prevention of DVT in patients with renal failure                                                 | HIT possible                                                                                       |
|                     |                     | Low-molecular weight heparins, e.g., enoxaparin (25, 26) | Prevention of ischemic complications of UA and NSTE-ACS, STE-ACS managed medically or with subsequent PCI | Accumulates in chronic renal failure                                                               |
|                     |                     | Low-molecular weight heparins, e.g., enoxaparin (27) | Acute pulmonary embolism                                                                                | Accumulates in chronic renal failure                                                               |
|                     | Fondaparinux (28)   | ACS                      |                                                                                                      | Positive effect on survival, thrombus formation on wires/balloons during (primary) PCI if no additional heparin is used, contraindicated in severe renal failure with a GFR <20 mL/min |
|                     | Fondaparinux (29)   | Prophylaxis of DVT in patients undergoing hip fracture surgery, hip replacement surgery and knee replacement surgery. | 50% VTE risk reduction compared with enoxaparin, no increase in clinically relevant bleeding Contraindicated in severe renal failure with a GFR <20 mL/min |
|                     | Rivaroxaban (30)    | VTE prophylaxis           |                                                                                                      | Easy administration, once daily, more effective compared with enoxaparin, same safety profile       |
|                     | Rivaroxaban (31)    | Non-valvular atrial fibrillation |                                                                                                      | Non-inferior to warfarin for the prevention of stroke or systemic embolism, same risk of major bleeding, however, less intracranial and fatal |

(Continued)
Table 1 | Continued

| Concept | Mechanism of action | Compound (key reference) | Indication | Benefits/Harms |
|---------|---------------------|--------------------------|------------|----------------|
| Rivaroxaban (32) | | Reduction of the risk of recurrent atherothrombotic events in patients with acute coronary syndromes | | Less cardiovascular death, myocardial infarction and stroke, but increased risk of major bleeding and intracranial hemorrhage, but not fatal bleeding |
| Apixaban (33) | | Non-valvular atrial fibrillation | | Compared with warfarin less ischemic strokes |
| Apixaban (34) | | VTE prophylaxis | | Superior to enoxaparin in preventing thrombosis |
| Direct thrombin (II) inhibition | | Lepirudin (35) | ACS | Low exposure rates, little information |
| | | Bivalirudin (36) | ACS | Survival benefit, however, signal of increased early stent thrombosis |
| | | Dabigatran (37), http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm | Reduction of risk of stroke and systemic embolism in Non-valvular atrial fibrillation | Compared with warfarin less hemorrhagic strokes, mild increase of GI bleeds, antibody-based antidote in development |
| | | Dabigatran (38) | Reduction of the risk of recurrence of DVT and pulmonary embolism | Compared with warfarin less hemorrhagic strokes, mild increase of GI bleeds, antibody-based antidote in development |
| | | Dabigatran (39) | Treatment of DVT and pulmonary embolism | Compared with warfarin less hemorrhagic strokes, mild increase of GI bleeds, antibody-based antidote in development |
| | | Argatroban (40) | Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; including patients undergoing PCI | Low exposure rates, low case numbers |
| Thrombolytic drugs/fibrinolytics | | Streptokinase (41) | Acute pulmonary embolism | Relatively low fibrin specificity, inexpensive |
| | | Streptokinase (42) | Acute coronary syndrome | Relatively low fibrin specificity, inexpensive |
| | | Alteplase (43) | Acute ischemic stroke | Recombinant tissue-type plasminogen activator with improved fibrin binding |
| | | Reteplase (44) | Acute coronary syndrome | longer half-life, better penetration into thrombus |
| | | Tenecteplase (45) | Reduction of mortality associated with acute myocardial infarction | higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA |

Selected references and selected indications are displayed. COX = cyclo-oxygenase, NSAID = non-steroidal anti-inflammatory drugs, kg = kilograms, ACS = acute coronary syndromes, PCI = percutaneous coronary intervention, UA = unstable angina, STE-ACS = ST elevation acute coronary syndrome, NSTE-ACS = non-ST elevation acute coronary syndrome, GFR = glomerular filtration rate, HIT = heparin-induced thrombocytopenia, ACS = acute coronary syndromes, DVT = deep venous thrombosis, VTE = venous thromboembolism, GI = gastro-intestinal, PAI-1 = plasminogen activator inhibitor type 1, t-PA = tissue-type plasminogen activator.

we understand acute vascular syndromes simply by plaque rupture that is driven by macrophages that are loaded with lipids, and proteolytically cleave a thin-cap fibroatheroma thus triggering platelet activation? Does that concept explain acute coronary syndromes in young subjects without significant vascular stenoses? Is thrombosis per se the trigger for all vascular occlusion, be it chronic or acute? Is vascular occlusion the sequela of deficient effectorosis, and are those mechanisms driven by a deficiency of natural antibodies? What are the recognition sites for natural antibodies in the circulation?
Which cells or cell fragments in the circulation are carrying oxidation specific epitopes, e.g., oxidized low-density lipoprotein (OxLDL) or malon-dialdehyde, and how do they function as danger associated molecular patterns? What is the role of nucleic acids, RNAse, and DNAse in thrombosis? Is NETting a preventable amplifier of acute thrombosis and the adverse vascular remodeling following thrombosis?

Are there potential therapeutic targets, upstream of mechanisms of thrombosis that might be applied without any potential bleeding risk? And might addressing those new targets prevent recurrence? Will we be able to identify a cellular program to those new targets prevent recurrence? Will we be utilizing therapeutic antagonists to control cellular responses to vascular injury? Will we be engineering vesels and vascular compartments of organ systems?

While bench-top research will address these questions, clinical research will complement advances both in drug-based trials and in interventional approaches. Since the PEITHO trial, the term of acute pulmonary revascularization has been coined in analogy to coronary revascularization, leading the way to interventional treatments as adjunct or stand-alone treatments for the pulmonary circulation. Similar developments have recently been initiated in chronic pulmonary vascular disease and will change treatment paradigms.

Taken together, thrombosis is an important mediator of vascular disease, but cannot be seen in isolation. Data suggest that it most often occurs as the consequence of a loss of vascular barrier function, for example, in the context of inflammation and rarely as a primary event. To comprehend mechanisms of vascular barrier function is another challenge of thrombosis research of the future. To understand thrombosis, we need to look beyond thrombosis.

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