UiT The Arctic University of Norway

Faculty of Health Sciences

ADAMTS13 and Myocardial Infarction: A Literature Review

Magnus Sandvik Edvardsen
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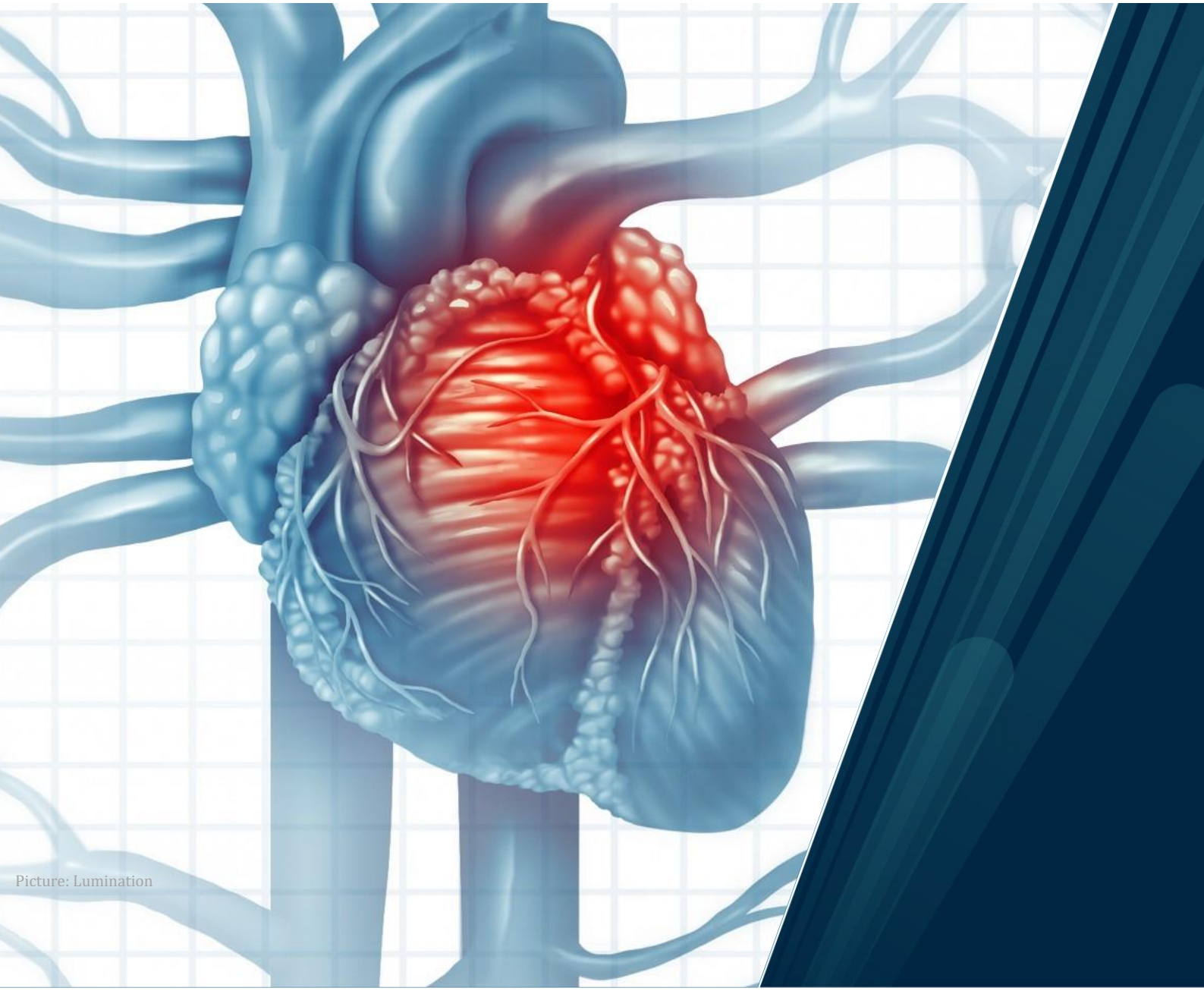
Main supervisor: Vânia Maris Morelli, researcher at Department of Clinical Medicine, UiT
Co-supervisor: Sigrid Kufaas Brækkan, professor at Department of Clinical Medicine, UiT
Co-supervisor: John-Bjarne Hansen, professor at Department of Clinical Medicine, UiT



Picture: Lumination

Preface

The aim of this master's thesis is to provide an overview of available case-control and cohort studies assessing the potential association between myocardial infarction and a specific protein named ADAMTS13.

My research career started in 2019 when I entered the Student Research Program in Medicine. I joined the Thrombosis Research Centre (TREC) research group at the Institute for Clinical Medicine, and had a full year of research in 2020. I found epidemiology difficult in the first years of my medical education but was quickly taking big strides as part of an accomplished team of researchers. My work has until this point led to two publications as first author; "*Plasma levels of von Willebrand Factor and future risk of incident venous thromboembolism*" and "*Combined effects of plasma von Willebrand factor and platelet measures on the risk of incident venous thromboembolism*".

Working on this thesis has allowed me to extend my knowledge on clinical epidemiology, and expand my insights on thrombosis beyond the world of venous thromboembolism. My future work, both in the clinic and in research, will certainly benefit from the knowledge I gained while working on this project. I started the work during the summer of 2021 and completed the thesis in May 2022.

I would like to extend my sincere gratitude to my supervisors, Dr. Vânia Maris Morelli, Professor Sigrid Kufaas Brækkan and Professor John-Bjarne Hansen, for their willingness to share their expertise, their constructive feedback and availability for proofreading. I feel very fortunate to be part of the TREC research group.

Magnus Sandvik Edvardsen

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Summary

Background: Myocardial infarction (MI) is the most common cause of death worldwide. Important modifiable risk factors have been unraveled and preventive measures established, but the disease burden remains substantial. Von Willebrand Factor (VWF) is a protein involved in hemostasis known to have platelet-recruiting ability according to molecular size. A disintegrin and metalloprotease with thrombospondin motif 13 (ADAMTS13) is responsible for the cleavage of VWF multimers, making it an important regulator of VWF thrombogenicity. As severe deficiency of ADAMTS13 is known to cause thrombosis in microvessels, it has been hypothesized that a slight to moderate decrease in ADAMTS13 levels leads to increased risk of MI.

Aim: To perform a literature review of existing case-control and cohort studies assessing the association between ADAMTS13 and MI.

Methods: The PubMed database was used to perform a literature search designed to retrieve all case-control and cohort studies on the association between ADAMTS13 and MI. Only studies that investigated ADAMTS13 as exposure and MI as outcome were included.

Results: Twelve studies were included, 10 case-control studies and 2 cohort studies. In the acute phase of MI, the vast majority of studies reported lower antigen or activity levels of ADAMTS13 in MI cases compared with control subjects. Findings were somewhat controversial when ADAMTS13 was measured several months/years after MI. A large prospective population-based cohort study found that individuals with low ADAMTS13 activity at baseline had increased risk of MI during 10 years of follow-up.

Conclusion: Existing literature suggests an association between ADAMTS13 and MI. In the acute phase of MI, patients have lower levels of ADAMTS13 compared with control subjects. ADAMTS13 activity also appears to be reduced in the years prior to the MI event. However, further research using a prospective study design (e.g., cohorts) is necessary to confirm the association between ADAMTS13 and risk of future MI.

Abbreviations

ACS – Acute coronary syndrome

ADAMTS13 – A disintegrin and metalloprotease with thrombospondin repeats type 1 motif, member 13

CHD – Coronary heart disease

CI – Confidence interval

HR – Hazard ratio

IHD – Ischemic heart disease

MI – Myocardial infarction

NSTEMI – Non-ST-elevation myocardial infarction

OR – Odds ratio

SNP – Single nucleotide polymorphism

STEMI – ST-elevation myocardial infarction

TTP – Thrombotic thrombocytopenic purpura

UAP – Unstable angina pectoris

ULVWF – Ultra-large von Willebrand Factor

VWF – von Willebrand Factor

WHO – World Health Organization

Background

Introduction

A myocardial infarction (MI) occurs when blood flow decreases or stops in the coronary artery of the heart, causing damage to the myocardium (the heart muscle) due to the lack of oxygen delivery.[1] The most common underlying mechanism of MI is the rupture of an atherosclerotic plaque in the vessel wall of a coronary artery, a process that ultimately leads to the formation of a thrombus that extends into the vessel lumen, where it can impede blood flow (Illustration 1).[2] The symptoms of MI frequently include chest discomfort, dyspnea, nausea and unexpected weakness.[3] The traditional risk factors for MI are an advancing age, hypertension, hypercholesterolemia, diabetes mellitus and smoking,[4] and except for an advancing age, all the other factors are modifiable. Despite the preventive measures to reduce the prevalence of these modifiable risk factors in the general population, data from the World Health Organization (WHO) indicates that MI is the most common cause of death worldwide.[5] To reduce the health burden of MI in society, novel insights into disease mechanism my help develop more effective measures for prevention and treatment of MI. Over the last decades, several novel potential risk factors for MI have been revealed, of which ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) appears to be one of the most relevant for the pathophysiology of MI. ADAMTS13 regulates the multimeric size and hemostatic function of von Willebrand factor (VWF) through the cleavage of platelet-hyperadhesive ultra-large VWF (ULVWF) multimers. Severe deficiency of ADAMTS13, either congenital or acquired, can result in an excess of ULVWF multimers and cause thrombotic thrombocytopenic purpura (TTP), a rare and potentially fatal disease characterized by platelet-rich microthrombi disseminated in the microcirculation. In the past two decades, the assessment of the antithrombotic role of ADAMTS13 has expanded beyond microcirculation, as slightly to moderately reduced ADAMTS13 levels were found to be associated with arterial cardiovascular disease, including MI.[6,7] A comprehensive literature review on the association between ADAMTS13 and MI, including the most recently published epidemiological studies, is a fundamental step to provide an updated overview and address the most important knowledge gaps related to the topic.

The aim of the present thesis was to conceive a comprehensive and updated review of the existing case-control and cohort studies on the association between ADAMTS13 and MI.

Myocardial Infarction – an overview

Acute coronary syndrome (ACS), also known as ischemic heart disease (IHD), is a disease entity comprised of MI and unstable angina pectoris (UAP).[2] It is characterized by inadequate blood flow to a segment of the myocardium, leading to death of heart muscle cells, with a potentially severe effect on the contractile function.[2] MI is typically further divided into infarctions with and without observable elevations of the ST-segment of electrocardiograms, STEMI (ST-elevation MI) and NSTEMI (non-ST-elevation MI). Complete obstruction of a coronary vessel often facilitates a transmural infarction, in which the resulting local electrolyte disturbances lead to this detectable alteration of electric impulse observed in electrocardiograms (i.e., elevation of the ST-segment).[8,9] Partial occlusion, on the other hand, typically leads to non-STEMI or UAP.[8] Currently, NSTEMIs comprise up to 75% of all MIs.[2] Although the differences between STEMI and NSTEMI are relevant in the process of diagnosing MIs, the two subgroups are treated according to the same principles in clinical settings, and often considered jointly in epidemiological research.[2]

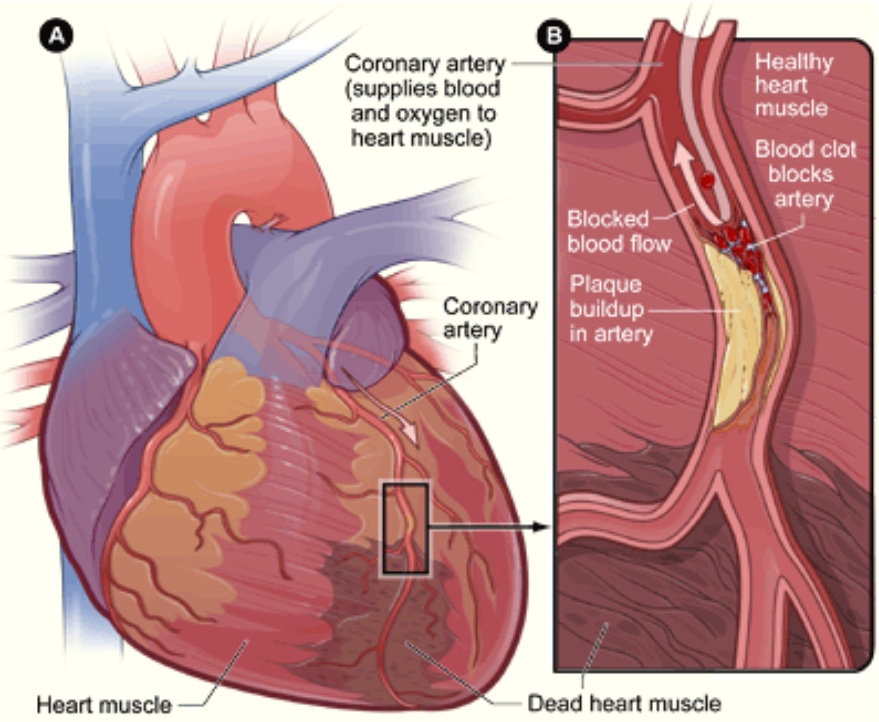

Illustration 1. **Illustration of myocardial infarction**. **A**. Macroscopic view of the heart. **B**. In a segment of the left anterior descending coronary artery, a thrombus has formed on an atherosclerotic plaque. The resulting cessation of blood flow leads to ischemia and necrosis in a part of the myocardium. (https://upload.wikimedia.org/wikipedia/commons/0/03/Heart_attack-NIH.gif)

Pathophysiology

MI rarely appears without an underlying condition. The process is usually initiated by development of an atherosclerotic plaque in the lining of an arterial vessel wall, a process which can take several years.[10] As the plaque grows, the vessel lumen shrinks, and increasing amounts of lipids are deposited in its core.[11] The lipid core, also known as necrotic core, has highly thrombogenic properties. MI often occurs when the surface of an atherosclerotic plaque is eroded or ruptured, leading to exposure of the highly thrombogenic core to the circulation.[3] As a result, the hemostatic system is stimulated and a platelet plug is formed on the inner lining of the vessel wall, ultimately growing into a platelet-rich thrombus. As the thrombus increases in size, blood supply to a part of the myocardium is compromised, eventually leading to ischemia and necrosis.[3] The process of atherosclerosis progression and thrombus formation is illustrated in detail in Illustration 2.[3]

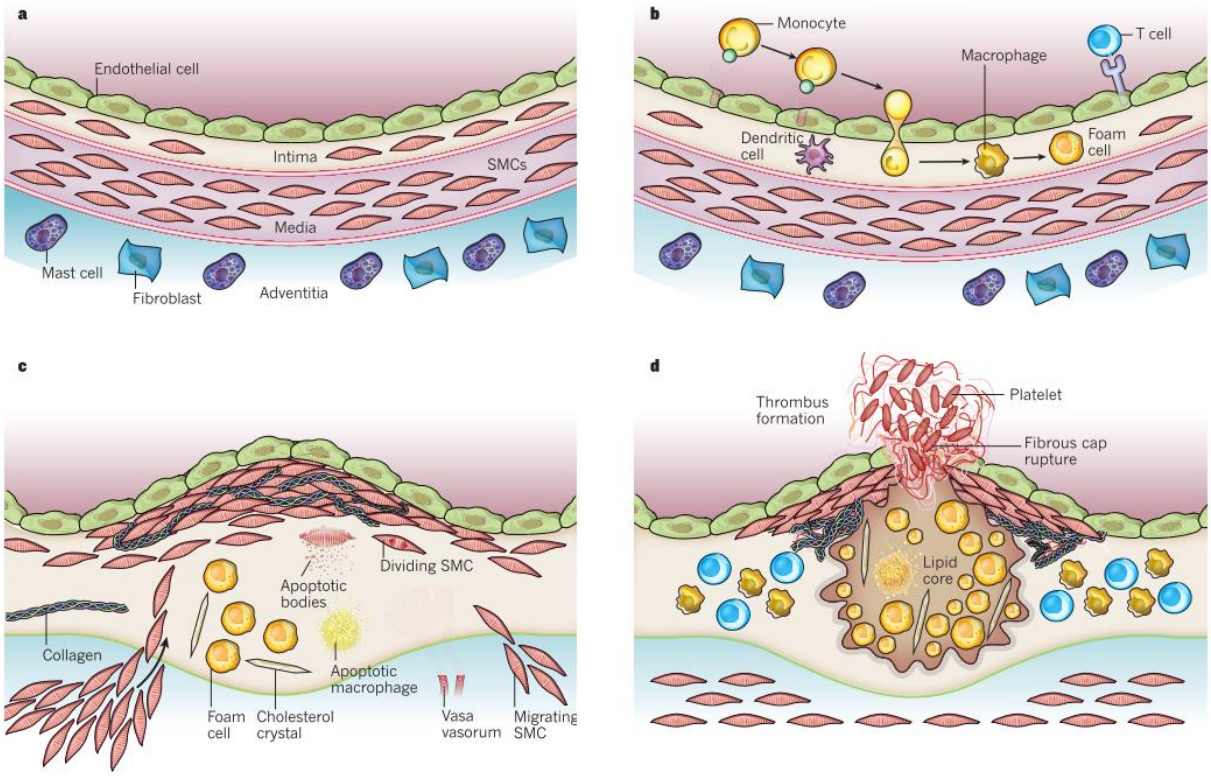

Illustration 2. Reprint with permission from *Libby et al. Nature (2011).*[11] **Stages in the development of atherosclerotic lesions**. **The normal muscular artery and the cell changes that occur during disease progression to thrombosis are shown. a**, The normal artery with the three layers (inner layer or tunica intima, middle layer or tunica media, and adventitia, the outer layer of arteries). **b**, The initial steps of atherosclerosis. **c**, Lesion progression. **d**, Thrombosis, the ultimate complication of atherosclerosis. SMC, smooth muscle cell.

Epidemiology

It is estimated that more than 90% of the risk for MI is due to modifiable risk factors.[12] Decades of extensive research have resulted in many novel insights regarding risk factors for atherosclerotic disease, which have propagated the successful implementation of preventive measures. Hypertension, hypercholesterolemia, smoking and diabetes mellitus are well-established modifiable risk factors for atherosclerotic diseases, including MI.[4] Hypertension is detrimental to the inner lining of the blood vessels, thereby facilitating atherosclerosis progression, and it also increases the work load of the heart, resulting in higher oxygen demand.[13] High levels of low-density lipoprotein cholesterol and smoking are found to increase the susceptibility of plaque rupture, leading to subsequent thrombus formation.[10] Diabetes mellitus is reported to drive a significant proportion of MI risk worldwide, as it is often accompanied by hypertension and increased amounts of proatherogenic and proinflammatory adipose tissue.[4] Over the past decades, the public health interventions with the use of blood pressure- and lipid-lowering medication along with general advice regarding lifestyle have resulted in effective mitigation of these modifiable risk factors, thereby leading to a reduction in MI incidence in high-income countries.[4,14,15] However, despite improved understanding and extensive efforts on implementation of preventive measures, risk factors now affect a broader part of the global population than in previous decades, including low- and middle-income countries. Atherosclerosis in coronary arteries is still the leading contributor to disease burden globally, assessed by disability-adjusted life-years.[16] It is estimated that IHD affects around 126 million individuals globally (1.72% of the world's population), with a prevalence rate of 1,655 per 100,000.[17] Recent data from the WHO further indicates that MI is the most common cause of death worldwide, accounting for around 9 million deaths each year, or 16% of all fatalities.[5,12]

High-income countries have reported declining incidence of MI over the last decades. For instance, in the United States, the incidence rates for hospitalization with acute MI and fatal coronary heart disease have declined by 5% per year in the period from 1987 to 2011.[18] The American Heart Association reported in 2019 that the proportion of "silent" MIs (an MI that goes clinically unnoticed) now accounts for nearly 50% of incident MIs, and a substantial proportion of MIs occur during hospitalization for another condition.[19] Similar findings have been reported from other countries.[4,14,15] Meanwhile, low- and middle-income countries have

shown a trend in the opposite direction, and are now experiencing an increasing proportion of deaths from cardiovascular disease.[16] Interestingly, the burden of traditional cardiovascular risk factors increases with income, while the incidence rates of MI have shown an inverse correlation (i.e., low- and middle-income countries tend to show a rise in the incidence of MI). In other words, it appears that an unequal distribution of preventive measures contributes to the present situation, where low- and middle-income countries suffer the largest disease burden.[3]

Scientific progress and novel risk factors

Despite improved understanding and prevention, MI continues to have a major impact on public health and healthcare systems worldwide.[4] Future perspectives therefore involve expanding the insights into novel mechanisms for atherosclerosis progression. Potential culprits under investigation include triglyceride-rich lipoproteins, disturbed sleep, physical inactivity, environmental stress, the gut microbiome and mutations in bone marrow stem cells.[4] Several of these seem to mediate atherosclerosis progression and activation of the hemostatic system through inflammatory pathways.[4,10,11] Altogether, an increasing knowledge on novel risk factors may facilitate a broader and more effective approach in MI prevention and treatment. It is worth noting that among the novel risk factors for MI currently under investigation, ADAMTS13, which is the cleaving protease of von VWF, emerges as one of the most relevant for the disease pathophysiology. The following sections of this thesis will address the historical aspects and the biology of this protease.

ADAMTS13

Thrombotic thrombocytopenic purpura and discovery of ADAMTS13

Thrombotic thrombocytopenic purpura (TTP) is a rare and potentially fatal disease first described in 1924.[20] It is characterized by several platelet-rich microthrombi disseminated in the microcirculation, eventually leading to ischemia in vital organs and subsequent death, if patients are left untreated.[21] The etiology of TTP remained elusive for many years, before a breakthrough was finally reached towards the end of the twentieth century. At this point it was suspected that VWF was an important culprit in the disease pathogenesis, as large amounts of ULVWF multimers, known to avidly recruit and activate platelets, were found in TTP patients.[22,23] In 1996, Tsai and Furlan independently discovered ADAMTS13, an enzyme responsible for regulating the multimeric size and hemostatic function of VWF

through the cleavage of the highly thrombogenic ULVWF multimers.[24,25] Following this, it was confirmed that deficiency of ADAMTS13, either inherited or acquired, is the cause of TTP.[26-28] The pathophysiological mechanism in the majority of adult TTP cases is that autoantibodies against ADAMTS13 render the enzyme severely impaired, resulting in an excess of ULVWF multimers on the surface of endothelial cells and in the circulation. The ULVWF bind spontaneously to platelets, forming thrombi within the microvessels, which induce platelet consumption, microangiopathic hemolytic anemia, and tissue ischemia, as illustrated in Illustration 3.[21]

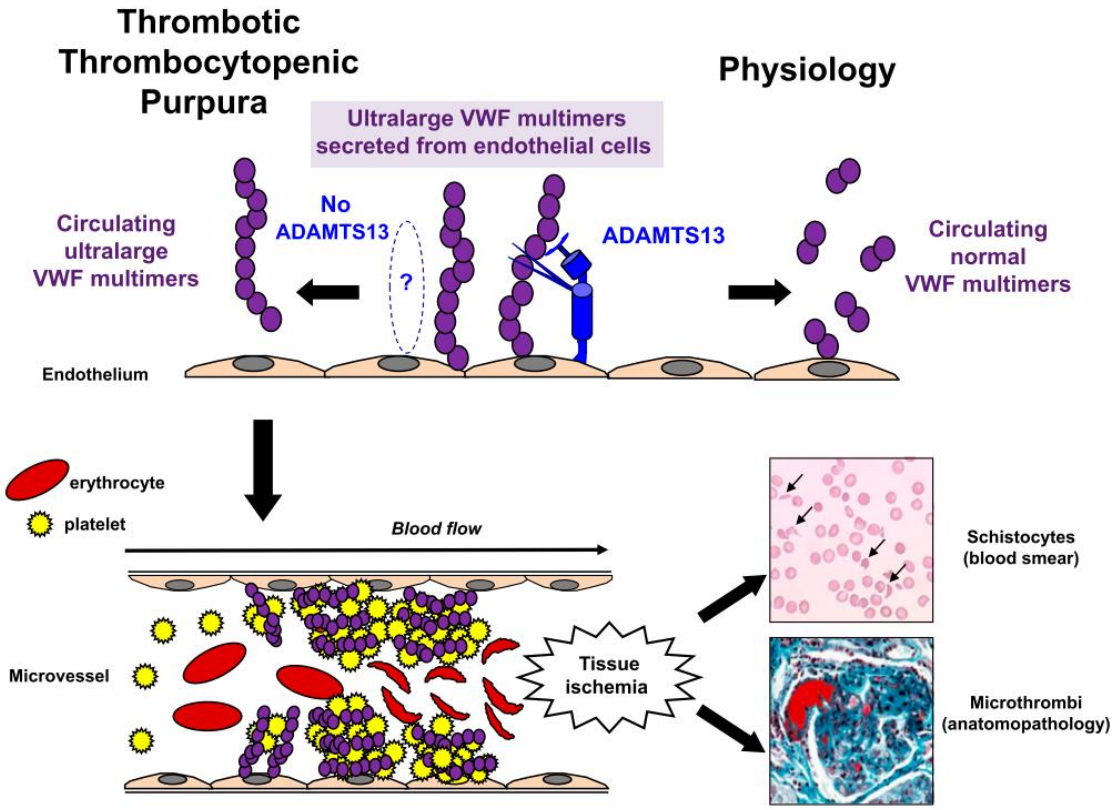

Illustration 3. Reprint with permission from *Joly et al. Blood (2017).*[21] **Pathophysiology for TTP**. In physiologic conditions, ultralarge VWF multimers released from endothelial cells are cleaved by ADAMTS13 in smaller VWF multimers, less adhesive to platelets. In TTP, because of the absence of functional ADAMTS13 (either absent by congenital defect or inhibited by specific autoantibodies), ultralarge VWF multimers are released into the blood and bind spontaneously to platelets to form aggregates within the arterial and capillary microvessels. The VWF–platelet aggregates are large enough to form microthrombi inducing tissue ischemia, platelet consumption, and microangiopathic hemolytic anemia (schistocytes on blood smear).

Protein synthesis and function

ADAMTS13 is mainly synthesized and secreted by hepatic stellate cells, with endothelial cells presumably contributing to a small proportion by constitutive secretion.[29,30] The ADAMTS13 gene, containing approximately 4.3 kilobases, is located at locus 34 in the long arm of chromosome 9 (9q34) and encodes the ADAMTS13 propeptide, which is exceptionally short at a mere 41 amino acid residues.[30] Mature ADAMTS13, however, is a polypeptide containing 1427 amino acid residues, with a molecular weight of 145 kDa.[31] After synthesis, mature ADAMTS13 is found to reside in the stellate cells of the liver interstitial area, from where it diffuses into capillaries and enters the blood stream.[29,30]

In contrast to other proteolytic metalloproteases, ADAMTS13 stands out by having only VWF as its exclusive protein substrate,[32] and there are no well-recognized physiologic inhibitors of ADAMTS13.[33] VWF is cleaved by ADAMTS13 in its A2 domain, between the Tyr1605 and Met1606 amino acids.[31] Circulating VWF usually takes a globular form, rendering the A2 domain inaccessible to ADAMTS13. Of note, in capillaries and small arteries, increased shear stress leads to unfolding of the VWF polymers, thereby providing access to the cleavage site.[31] Additionally, an in vitro study found that globular VWF also exposes a binding site for ADAMTS13, which to a certain degree allows proteolysis also under low-shear conditions.[34] VWF promotes hemostasis by binding platelets with the A1 domain, leading to platelet activation and platelet plug formation.[33] Interestingly, ADAMTS13 has more recently been found to be conformationally activated by VWF, depicting a reciprocal relationship between the two proteins.[35,36] Illustration 4 shows the molecular structure of VWF and ADAMTS13 in detail.

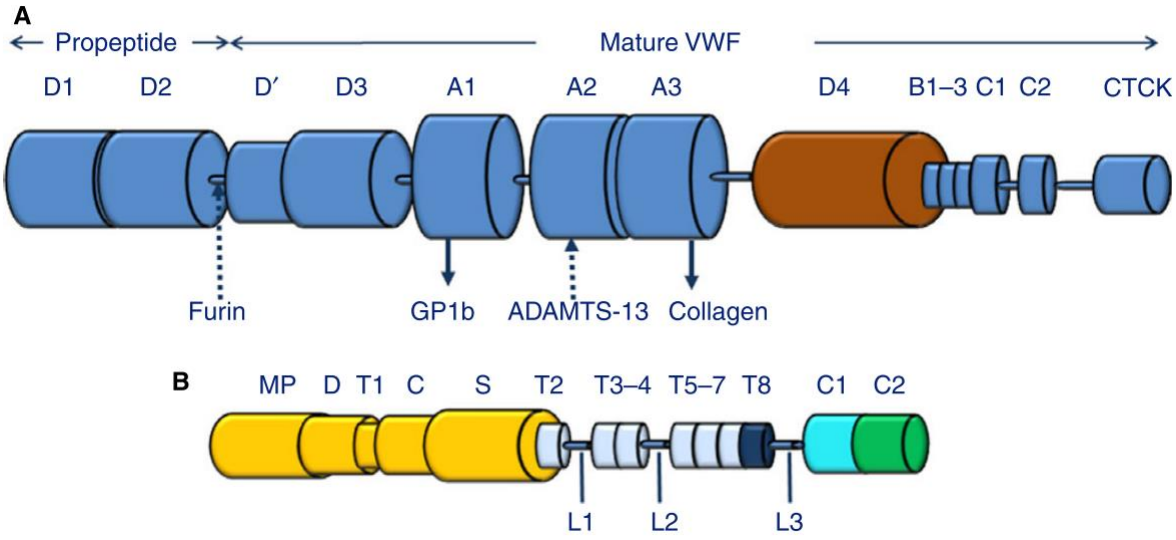

Illustration 4. Reprint with permission from *South et al. J Thromb Haemost (2018)*.[33] **The domain organization of von Willebrand factor (VWF) and ADAMTS13**. **A**. VWF contains multiple functional domains, beginning with domains D1 and D2 at the protein N-terminus. These domains form the propeptide, and are removed by furin cleavage to generate the mature VWF monomer. The D0 and D3 domains, which are involved in multimer formation, proceed the three central A domains. The A1 domain contains the platelet glycoprotein (GP) 1b-binding motif, which is exposed under conditions of increased shear stress. Under these conditions, the ADAMTS13 cleavage site within the A2 domain is also exposed. The A3 domain contains the constitutively exposed collagen binding site responsible for VWF tethering at sites of vascular injury. The D4 domain, shown in brown, binds to the C-terminal domains of ADAMTS13 and initiates ADAMTS13 conformational activation. The remaining C-terminal domains are annotated as they most commonly appear in the literature, with the C-terminal cysteine knot (CTCK) domain, required for dimer formation, at the C-terminus. **B**. ADAMTS13 consists of the N-terminal metalloprotease (MP), disintegrin-like (D), thrombospondin (TSP) 1 (T1), cysteine-rich (C) and spacer (S) domains (yellow). The C-terminal CUB1 (teal) and CUB2 (green) domains are connected to the proximal domains through seven further TSP repeats (TSP2–7 in light blue, and TSP8 in dark blue). Three flexible linker regions (L1, L2, and L3) allow the formation of the ADAMTS-13 closed conformation.

Antigen level and activity

In plasma, ADAMTS13 antigen level is usually measured by enzyme-linked immunosorbent assay (ELISA).[37] For the measurement of ADAMTS13 activity, several methods exist. Currently, the most commonly used method is a fluorescence resonance energy transfer (FRET) assay, called FRETS-VWF73, which uses a modified fragment of VWF (a synthetic 73-amino-acid peptide) that serves as a specific substrate for ADAMTS13, allowing measurement of the enzyme activity in plasma.[37] Antigen and activity of ADAMTS13 are normally strongly correlated in healthy populations and are affected by both inherited and acquired factors.[38] On the genetic side, it was discovered that single-nucleotide polymorphisms (SNPs) in the ADAMTS13 gene are responsible for a significant proportion of activity variability in the general population.[39] More recently, genome-wide association studies have further revealed several influential genes, culminating in at least 60% heritability of ADAMTS13 antigen level.[40,41]

Plasma ADAMTS13 is found to remain quite stable in human individuals, but it is prone to significant reduction upon pathological conditions such as liver disease, cancer and sepsis.[42] Physiological conditions, including an advancing age and pregnancy, as well as

environmental factors (e.g., smoking) are also found to be associated with lower ADAMTS13 plasma antigen and activity.[41-43]

Rationale to study ADAMTS13 in MI

Given the evident prothrombotic nature of ADAMTS13 deficiency, as observed in TTP patients, it has been hypothesized that a slight to moderate decrease in antigen level or activity of ADAMTS13 may also result in a prothrombotic state. Further, both inflammatory pathways and environmental stress are known to influence ADAMTS13[42,43] and are currently under investigation as potential culprits in the pathogenesis of MI. Altogether, a role of ADAMTS13 in the development of arterial thrombosis is biologically plausible. Following this, a considerable number of studies assessing the potential association between ADAMTS13 and various thrombotic diseases, including MI, have been published in the recent years. A comprehensive literature review on the association between ADAMTS13 and MI, including the most recent epidemiological studies, is a fundamental step to provide an updated overview and address the most important knowledge gaps related to the topic.

Aim

The aim of the present thesis was to provide a comprehensive review of existing case-control and cohort studies on the association between ADAMTS13 and MI.

Methods

Search strategy

To identify relevant studies assessing the association between ADAMTS13 and MI, a structured search designed to retrieve all articles of interest was performed. On April 27th 2022, PubMed was searched using the following terms:
((ADAMTS13) OR (ADAMTS-13)) AND ((myocardial) OR (coronary))

There was no date restriction in the search strategy. Therefore, all studies published before the search date (April 27th, 2022) were included in the search. The electronic search was supplemented by a manual search of the reference lists of all included studies.

Study selection

Search results were initially screened by title and abstract using the inclusion and exclusion criteria listed below, and after this process the remaining articles were read in full. The present literature review included only studies restricted to humans, comprised of an adult population, with ADAMTS13 investigated as the exposure and MI as the outcome of interest. Only studies using a case-control and cohort design were included. Exclusion criteria: a study design other than a case-control or a cohort, studies where ADAMTS13 was not addressed as exposure, studies where MI was not addressed as singular outcome (e.g., including combined assessment of MI and UAP), studies with full text not available, and studies published in a language other than English.

Data extraction

In order to present all included studies coherently, the following data were extracted and presented in a tabular format: first author, year of publication, country where the study was performed, study design, number of participants, ADAMTS13 measurement method, time of ADAMTS13 measurement in relation to the outcome (i.e., on hospital admission due to acute MI, or time before or after the MI), and the main findings.

Results

The search strategy yielded 301 records. After applying the inclusion and exclusion criteria, 11 studies were identified as relevant case-control or cohort studies, and 1 additional study was identified through reference assessments. The flowchart of the search strategy and inclusion process is shown in Figure 1.

Ten case-control studies compared ADAMTS13 level or activity in MI patients and control subjects. Five of these studies measured ADAMTS13 antigen or activity in blood samples drawn at the acute phase of MI,[6,44-47] three sampled blood several months/years after the event,[48-50] while two studies sampled blood both in the acute phase and a few months after

MI.[51,52] Additionally, two prospective cohort studies were identified. One cohort followed a group consisting of individuals with peripheral artery disease,[53] while the other followed a group derived from the general population.[7] The included studies are presented in Figure 2 and Tables 1 and 2.

ADAMTS13 in the acute phase of MI

A total of 7 case-control studies compared ADAMTS13 antigen or activity in blood samples obtained from controls and cases in the acute phase of MI, and the majority of the studies found that low antigen or activity of ADAMTS13 was associated with MI (Table 1). In fact, 5 studies found that MI patients had significantly lower ADAMTS13 levels than control subjects. First, Kaikita and colleagues reported in 2006 that 41 MI patients had significantly lower antigen and activity levels of ADAMTS13 compared with 30 patients with stable angina and chest pain syndrome.[44] A year later, Matsukawa and colleagues presented similar findings, with MI patients having lower antigen levels of ADAMTS13 compared with age- and sex-matched patients undergoing elective cardiac catheterization.[47] Horii and colleagues next set out to replicate these findings, while also comparing activity levels of ADAMTS13 in blood samples drawn from the femoral vein, coronary sinus vein and the aortic root. However, they found no significant differences between cases and age-matched controls, and also reported that the activity levels of ADAMTS13 were similar for the three sites of blood sampling.[51] In a study of Italian women, Peyvandi and colleagues compared antigen levels of ADAMTS13 in 138 MI patients with 199 age-matched healthy controls and detected no significant difference. In fact, the MI patients had slightly higher levels of ADAMTS13, with antigen levels in the highest tertile yielding an odds ratio (OR) of 1.6 (95% confidence interval [CI] 0.9-2.9) for MI, compared with the lowest tertile.[45] In the largest case-control study on ADAMTS13 levels in acute MI, Rutten and colleagues found that 1026 MI patients had lower antigen levels of ADAMTS13 than healthy controls. For those with ADAMTS13 antigen levels in the highest quartile, the investigators found an OR of 0.6 (95% CI 0.5-0.8) for MI, compared with participants with ADAMTS13 activity in the lowest quartile.[6] Yan and colleagues next reinforced the existing evidence by finding significantly lower ADAMTS13 activity levels in MI patients, compared with controls.[46] Finally, a recent study by Al-Masri and colleagues compared ADAMTS13 antigen levels of 80 MI patients (at hospital admission, 2-3 days later and 3 months later) with levels measured in healthy age-, sex- and BMI-matched control subjects. Unsurprisingly, the authors reported that patients had

significantly lower levels of ADAMTS13 antigen than controls in the acute phase of MI, both at hospital admission and after 2-3 days.[52]

ADAMTS13 outside the acute phase of MI

Five case-control studies compared antigen or activity levels of ADAMTS13 between control subjects and MI patients in blood samples drawn several months/years after the event (Table 2). In these studies, the findings were more discordant than those in the acute MI setting. Interestingly, Chion and colleagues found in a large case-control study that 560 MI patients had higher antigen levels of ADAMTS13 >6 months after the event, when compared with 646 healthy controls. ADAMTS13 antigen in the highest quartile yielded an OR of 1.26 (95% CI 1.10-2.22) for MI, compared with those in the lowest quartile.[48] A year later, Crawley and colleagues performed a similar study on 447 MI patients and 472 age- and sex-matched healthy controls, and found that MI cases had significantly lower antigen levels of ADAMTS13. ADAMTS13 in the top tertile versus the lowest tertile yielded an OR of 0.52 (95% CI 0.31-0.85) for MI, compared with those in the lowest tertile.[49] Horii and colleagues measured ADAMTS13 activity 6 months after MI revascularization, and found no difference between MI cases and control subjects, which was in accordance with their findings from the acute phase.[51] When blood samples were drawn more than 3 years after the MI event, Andersson and colleagues found in a study comprising only women, that the cases still had significantly lower ADAMTS13 antigen compared with controls. ADAMTS13 antigen in the lowest quartile yielded an OR of 1.8 (95% CI 1.1-3.0) for MI, compared with those in the highest quartile.[50] Finally, Al-Masri and colleagues, also mentioned above, found that the difference in ADAMTS13 antigen levels between controls and MI cases observed in the acute phase had disappeared 3 months after the event.[52]

Two cohort studies prospectively assessed whether ADAMTS13 levels were associated with future MI (Table 2). In a large cohort based on the Rotterdam Study, Sonneveld and colleagues included 5688 participants from the general population, aged >55 years with no history of coronary heart disease (CHD) or stroke at baseline. ADAMTS13 activity was measured at baseline, and the median follow-up time was 9.7 years. Regression analyses revealed that participants with ADAMTS13 activity in the lowest quartile had significantly increased risk of MI and CHD mortality, with a hazard ratio (HR) of 1.42 (95% CI 1.07-1.89), compared with those in the highest quartile.[7] Further, Green and colleagues studied a cohort consisting of 595 patients with peripheral artery disease, where they sampled blood every 2

months over the course of 3 years. When they compared ADAMTS13 antigen levels between those who developed MI during follow-up and those who did not, no significant difference was found.[53]

Discussion

General discussion

In the present thesis, case-control and cohort studies assessing the association between ADAMTS13 and MI were summarized in a literature review. The results consistently point towards a decrease in ADAMTS13 antigen and activity in the acute phase of MI. Studies assessing the potential association several months/years after MI presented more conflicting results, but also here a slight majority of the results pointed towards a reduction of ADAMTS13 levels in MI cases. A large population-based cohort found that low ADAMTS13 activity resulted in significantly increased risk of future MI. Overall, the literature suggests a role of ADAMTS13 in the development of MI.

In recent years, two Mendelian randomization studies have assessed the association between ADAMTS13 and MI. This study design uses genetic variants associated with a modifiable exposure to explore whether the exposure is causally associated with an outcome. On the basis that genes are inherited randomly, this method resembles randomized controlled trials (RCTs), which are the gold standard when evaluating causality.[54] Schooling and colleagues found in 2018 that low ADAMTS13 activity, as predicted by three genetic variants, was associated with IHD.[55] Next, Ye and colleagues verified this finding and also found that genetically predicted low activity of ADAMTS13 was associated with MI.[56] Based on the findings from the Mendelian randomization studies, it seems that ADAMTS13 is causally related to MI, and that an increase in the protease activity has the potential to contribute to MI prevention.

When a blood vessel is damaged and bleeding occurs, VWF is known to promote hemostasis by a few different mechanisms. First, it promotes the adhesion of platelets to the site of damage and aggregation of platelets to each other, assisting in the formation of a platelet plug.[57] Next, VWF is known as the carrier and protector of coagulation factor VIII, which is an important role in hemostasis, as factor VIII is key for thrombin generation, a

process that ultimately leads to fibrin formation stabilization of blood clots.[57] VWF normally circulates in closed conformation, but unfolds from its globular form upon increased shear stress, resulting in exposure of its platelet-binding domains.[58] As increased shear stress is seen both in sites of vessel rupture and in stenotic arteries, it is likely that atherosclerotic plaque results in a locally increased platelet-binding activity of VWF.[58] It is therefore biologically plausible that increased VWF activity in the presence of atherosclerotic coronary arteries has an influential role in MI pathogenesis. In support of this, thrombi formed in coronary arteries are found to be rich in VWF and platelets.[59]

During the last couple of decades, an association between high VWF levels and MI has become clear, with studies finding elevated VWF levels in MI cases both before, during, and after the event.[60] Further, Mendelian Randomization studies suggest that this association is causal.[61] When these findings are evaluated in light of the ones from the present thesis, a substantial body of evidence points towards an influential role for the VWF/ADAMTS13 axis in MI pathogenesis. An imbalance in this important axis for hemostasis may be the result of abundant secretion of prothrombotic large VWF multimers, and/or inadequate amount of ADAMTS13 activity. In agreement with this hypothesis, researchers who assessed the ratio between VWF and ADAMTS13 found that MI patients had a higher ratio compared with control subjects.[6,46,47,51,52] Moreover, Pedrazzini and colleagues further reported a local VWF/ADAMTS13 imbalance in the coronary circulation of MI patients, when compared with blood from other sites in circulation.[62]

In light of the current literature, which suggests a causal association between ADAMTS13 levels and MI,[55,56] a possibility of modifying the VWF/ADAMTS13 axis to reduce thrombotic tendency emerges. In fact, the idea of using ADAMTS13 as a therapeutic agent has already been suggested by several researchers, as growing evidence has suggested a detrimental impact of an imbalance in the VWF/ADAMTS13 axis on arterial thrombosis.[63,64] Four experimental animal studies have investigated the infusion of recombinant human ADAMTS13 (rADAMTS13) as a therapeutic agent in MI. De Meyer and colleagues found that wild type mice infused with rADAMTS13 had smaller infarctions with less complications compared with mice that did not receive this treatment,[65] a finding which was replicated twice by other investigators.[66,67] However, using a porcine model of myocardial ischaemia-reperfusion, Eerenberg and colleagues found that administration of rADAMTS13

did not have an effect on infarct size or haemorrhage.[68] The possibility of targeting the VWF/ADAMTS13 axis for prevention of MI is, however, yet to be explored.

Methodological considerations

The main strengths of the present thesis include the structured literature search and predefined criteria for inclusion, enhancing the likelihood of a complete review of the available literature on the topic. Further, as ADAMTS13 is a relatively recent discovery, it was not necessary to impose any search restriction regarding publishing year. Crosscheck of references was also performed to identify studies which could potentially have been missed in the literature search, further improving the probability of a complete overview. The thesis also has limitations that merit attention. The literature search and screening of records was performed by only one person, which could have led to missed papers. A few publications had titles/abstracts which fulfilled the criteria for further assessment, but they were not available in full text or in English language. If these studies investigated the same research question but were systematically different from the included studies, it would introduce a possibility for selection bias in the thesis. It is, however, rather unlikely that these few papers would present drastically different findings compared with the included studies, to the degree where it would alter the conclusions of the present thesis.

The included studies are not without methodological issues. Case-control studies have some limitations prohibiting causal interpretations from potential associations. First, case-control studies suffer the important drawback that the blood samples were drawn after the occurrence of MI. Without a clear overview of the temporal sequence between the exposure and outcome under investigation, it is not possible to evaluate whether low ADAMTS13 level is a risk factor for MI, or simply a consequence of the MI event. This phenomenon is referred to as reverse causation. Next, there is a possibility that the association reported in the included papers was due to confounding. For instance, inflammation could be associated with both reduction of ADAMTS13 levels and MI, thereby leading to a spurious association between ADAMTS13 and MI in the analyses.[69] Included studies were heterogenous with regards to adjustment for potential confounders, but the findings did not systematically vary between adjusted and unadjusted analyses. Finally, some of the studies involved small sample sizes, which could have limited the precision of the estimates, thereby increasing the uncertainty around their results.[70]

The included prospective cohort studies avoid the issue related to reverse causation, but as the case-control studies, they are also susceptible to confounding. Indeed, even after extensive adjustments, residual confounding due to unknown confounding factors cannot be ruled out in observational studies.[71] One of the cohorts collected blood samples at baseline and had a median follow-up of almost 10 years. As activity levels of ADAMTS13 are modifiable, it is likely that the measured levels would not have been representable throughout the follow up period, introducing the possibility for misclassification. However, it is reasonable to assume that this would affect all participants in the same way, both those with and without MI. In other words, it would be a non-differential misclassification, which would result in a weakening of the potential association between ADAMTS13 activity and MI through regression dilution.[72]

Conclusion

In conclusion, existing case-control and cohort studies point towards an association between ADAMTS13 and MI. In the acute phase of MI, cases have lower antigen and activity levels of ADAMTS13 compared with controls. In studies evaluating ADAMTS13 outside the acute phase of MI, the results were more controversial but, in general, suggest an association between a low ADAMTS13 levels and increased risk of MI. Further research involving prospective cohort studies preferably combined with a Mendelian randomization approach is warranted to confirm the role of ADAMTS13 in the development of MI.

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Tables and Figures

Table 1. Included acute phase studies. Case-control studies assessing the association between ADAMTS13 and myocardial infarction (MI) in the acute phase.

Author, year, Country	Study design, participants	ADAMTS13 measurement	Main findings
Kaikita et al. 2006 Japan (44)	Case-control 41 MI, 30 controls	Antigen and activity On hospital admission	ADAMTS13 activity and antigen were lower in MI patients than in controls. Antigen: 799±29 vs. 967±31 mU/mL, p < 0.0002. Activity: 768±27 vs. 936±29, p=0.0014.
Matsukawa et al 2007 Japan (50)	Case-control, cohort 92 MI, 40 controls	Antigen On admission + 2 weeks	Lower ADAMTS13 antigen in MI patients than in controls (0.63 vs 0.94 U/mL, p<0.0001) at admission. Lowest after 3 days. Those with less increase of ADAMTS13 level between admission and day 3 had increased risk of recurrent thrombosis.
Horii et al, 2008 Japan (51)	Case-control 26 MI, 37 controls	Activity Before PCI and 6 months after	In the acute phase of MI, there was no significant difference in ADAMTS13 activity between MI cases (55%±22) and age-matched controls (51%±15), p>0.05.
Peyvandi et al, 2010 Italy (45)	Case-control 138 MI, 199 controls Women < 45 years	Antigen 0-3 days after event	Statistically non-significant increased ADAMTS13 antigen in cases compared with controls. ADAMTS13 in T3 vs T1: OR 1.6 (95% CI 0.9-2.9).
Rutten et al, 2015 China, Italy, UK (6)	Case-control 1026 STEMI, 652 controls	Antigen <6 hours after MI	Lower ADAMTS13 antigen in STEMI patients compared with controls. ADAMTS13 in Q4 vs Q1: Unadjusted OR 0.6 (95% CI 0.5-0.8) and multivariable adjusted OR 0.8 (95% CI 0.6-1.0) for STEMI.
Yan et al, 2017 China (46)	Case-control 146 MI, 105 controls	Activity <12 hours after MI	Lower ADAMTS13 activity in MI patients compared with controls. 44.9% ±0.8 vs 48.8% ±1.2, p<0.01.
Al-Masri et al, 2020 Saudi Arabia (52)	Case-control 80 MI, 36 controls	Antigen On admission, after 2-3 days, at 3 months	MI cases had lower ADAMTS13 antigen than controls on admission and 2-3 days post MI (19.55 and 19.71 vs 24.22 µIU/L, both p<0.05).

Green color indicates lower ADAMTS13 levels in MI cases. Gray indicates no significant association.

ADAMTS13, a disintegrin and metalloprotease with thrombospondin motif type 13; **PCI,** percutaneous coronary intervention; **T**, tertile; **OR**, odds ratio; **CI**, confidence interval; **STEMI**, ST-elevation myocardial infarction; **Q**, quartile.

Table 2. Included studies outside the acute phase. Case-control and cohort studies assessing the association between ADAMTS13 and myocardial infarction (MI) outside the acute phase.

Author, year, Country	Study design, participants	ADAMTS13 measurement	Main findings
Chion et al. 2007 Netherlands (47)	Case-control 560 MI, 646 controls Men between 18-70 y	Antigen >6 months after MI	Higher ADAMTS13 antigen in MI patients. For those with ADAMTS13 in Q4 vs Q1: OR 1.26 (95% CI 1.10-2.22) for MI.
Crawley et al, 2008 UK (48)	Case-control 447 MI, 472 controls	Antigen 3-9 months after MI	Lower ADAMTS13 antigen in MI patients. For those with ADAMTS13 in T3 vs T1: OR 0.51 (95% CI 0.31-0.85) for MI. OR 0.72 (95% CI 0.58-0.88) per standard deviation increase.
Horii et al, 2008 Japan (51)	Case-control 26 MI, 37 controls	Activity Before PCI and 6 months after	Six months post MI, there was no significant difference in ADAMTS13 activity between MI cases (51%±19) and age-matched controls (51%±15), p>0.05.
Andersson et al, 2012 Netherlands (49)	Case-control 205 MI, 638 controls Women between 18-49 y	Antigen 38-117 months after MI	Lower ADAMTS13 antigen in MI patients compared with controls. ADAMTS13 in Q1 vs Q4: OR 1.8 (95% CI 1.1-3.0) for MI.
Al-Masri et al, 2020 Saudi Arabia (52)	Case-control 80 MI, 36 controls	Antigen On admission, after 2-3 days, at 3 months	Three months post MI, there was no significant difference in ADAMTS13 antigen levels between MI cases (23.11±5.11 µIU/L) and controls (24.22±5.59 µIU/L), p>0.05.
Sonneveld et al, 2016 Netherlands (7)	Cohort 5688 participants	Activity At baseline.	Low ADAMTS13 activity at baseline yielded increased risk of future MI and CHD mortality. ADAMTS13 in Q1 vs Q4: Multivariable adjusted HR 1.42 (95% CI 1.07-1.89) for MI and CHD mortality.
Green et al, 2017 USA (53)	Cohort 595 patients with peripheral artery disease	Antigen Every 2 months for up to 3 years	No difference in ADAMTS13 antigen in those with and without MI. 1.01 (0.81-1.14) vs 1.00 (0.83-1.18) µg/mL, p=0.57.

Green color indicates lower ADAMTS13 levels in MI cases. Gray indicates no significant association. Red indicates higher ADAMTS13 levels in MI cases.

ADAMTS13, a disintegrin and metalloprotease with thrombospondin motif type 13; **Q**, quartile; **OR**, odds ratio; **CI**, confidence interval; **T**, tertile; **PCI**, percutaneous coronary intervention; **CHD**, coronary heart disease; **HR**, hazard ratio.

Figure 1. PubMed search and inclusion process. PubMed search yielded 301 records. A total of 290 studies were excluded according to pre-defined exclusion criteria. One study was identified by manual search of the reference lists of included studies. Twelve studies were included: Ten case-controls and two cohort studies.

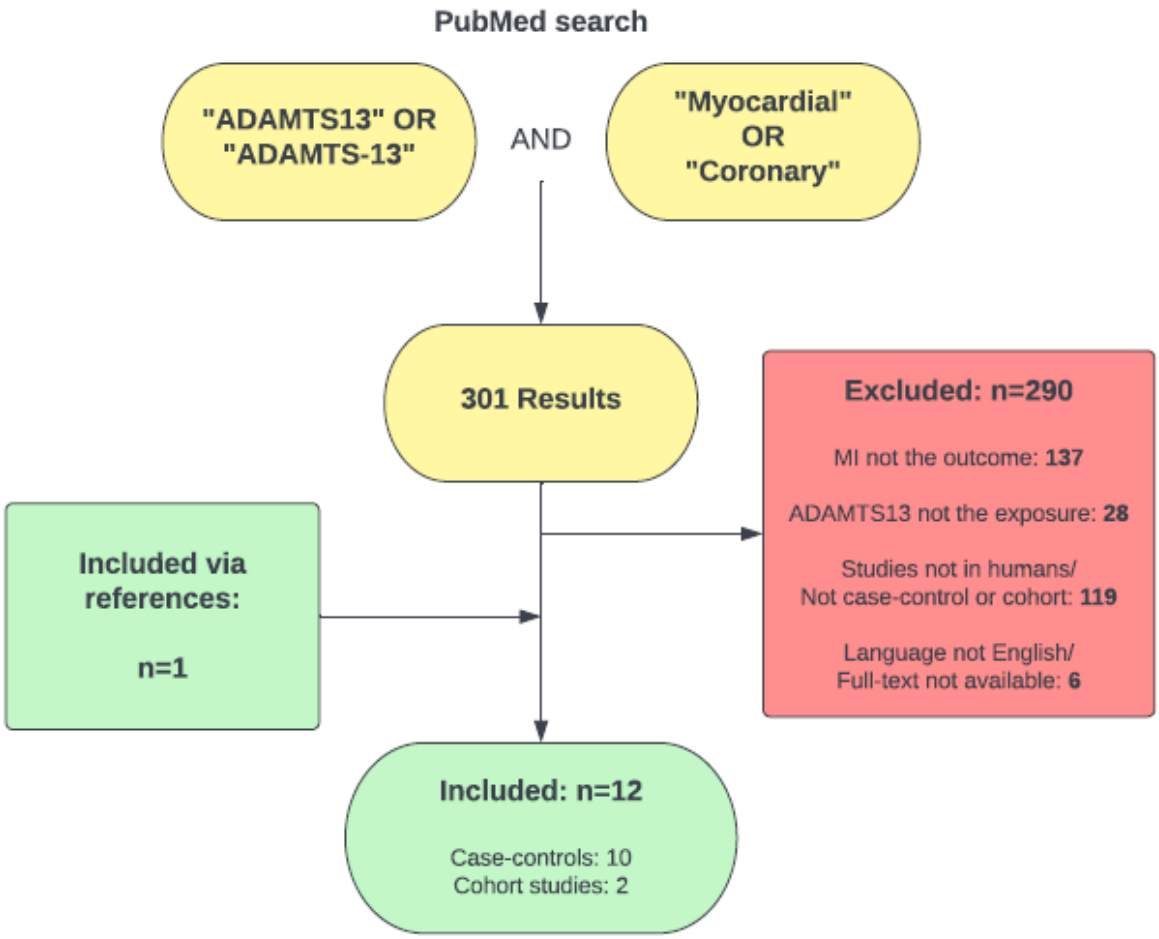

Figure 2. Included studies by study design and time of ADAMTS13 measurement in relation to the outcome (i.e., myocardial infarction). ADAMTS13, a disintegrin and metalloprotease with thrombospondin motif type 13; **MI**, myocardial infarction.