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Review

Microparticles and cardiovascular diseases

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Abstract

Microparticles are a distinctive group of small vesicles, without nucleus, which are involved as significant modulators in several physiological and pathophysiological mechanisms.

Plasma microparticles from various cellular lines have been subject of research. Data suggest that they are key players in development and manifestation of cardiovascular diseases and their presence, in high levels, is associated with chronic inflammation, endothelial damage and thrombosis. The strong correlation of microparticle levels with several outcomes in cardiovascular diseases has led to their utilisation as biomarkers. Despite the limited clinical application at present, their significance emerges, mainly because their detection and enumeration methods are improving.

This review article summarises the evidence derived from research, related with the genesis and the function of microparticles in the presence of various cardiovascular risk factors and conditions. The current data provide a substrate for several theories of how microparticles influence various cellular mechanisms by transferring biological information.

(148 words)

Keywords: Microparticles, Cardiovascular, Inflammation, Thrombosis, Atherosclerosis, Heart failure

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Key messages

- Formation of microparticles, after physiological or pathophysiological cellular stimulation, may activate mechanisms related to coagulation, inflammation and angiogenesis, mainly by transferring biological information from the paternal cells.
- Data from research suggest that risk factors for cardiovascular diseases are associated with high levels of microparticles from different cellular lines.
- Manifestation and activity of cardiovascular diseases partly regulated by the presence and levels of microparticles.
- Utilisation of microparticles as biomarkers emerges and there is evidence that their levels might also have prognostic value for several cardiovascular pathological conditions.

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1.Introduction

Both eukaryotic and prokaryotic cells, under the influence of several external or internal factors, can produce small vesicles. These vesicles are enclosed in a biphospholipid layer and contain part of the paternal cytosol(1). Part of this heterogeneous population of cell-derived vesicles are the microparticles which serve as a disseminated storage pool of active biological molecules(2). For long time after their discovery, microparticles were considered as cell debris, result of biological processes without any significant meaning. However, technological advantages of their detection and characterisation stimulated research for investigation of their roles in various clinical situations(3).

The current evidence suggests that microparticles formation from different types of cells, in normal circumstances, is not just a passive process following apoptosis, necrosis or cellular dysfunction but is a balanced mechanism that promotes communication between various cellular types. Microparticles influence vital physiological functions such as inflammation, coagulation, apoptosis and cell differentiation and may trigger pathophysiological mechanisms which contribute to the genesis of atherosclerosis and thrombosis, the cornerstones for the development of cardiovascular disorders(4). Apart from the current role as reflectors/biomarkers of certain cardiovascular and other diseases, microparticles have been proposed as potential targets in order to regulate various conditions with auto-immune or thrombotic causality(5).

This review article summarises the evidence derived from research, related with the genesis and the function of microparticles in the presence of various cardiovascular risk factors and conditions.

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2. Definition and Nomenclature

Knowledge on extracellular vesicles have significantly expanded over the last 2 decades. Even at the last meeting of International Society of Extracellular Vesicles in 2018, there was no definitive consensus about the definition of microparticles(6).

The broad term to describe particles released from cells by natural process such that their cytosol is enclosed by a lipid bilayer and lacking synthetic capacity, is “extracellular

vesicles". The term 'microparticles' has been used for a variety of extracellular vesicles in the past. The distinction of exosomes and ectosomes (Figure 1) is important in order to approach the nature of microparticles. Exosomes are formed after an inward bledding of the plasma membrane and stored into a bigger intracellular vesicle, the multivesicular body. Later, exosomes can be released in the extracellular environment by exocytosis. On the contrary, ectosomes are vesicles which directly released from the paternal cell by outwards rearrangement of the cellular membrane(7). Of note, there is a significant overlap regarding size (diameter), membrane protein composition and cellular origin of the extracellular vesicles which at present makes difficult their categorisation(8). Even their characterisation as ectosomes or exosomes is generally not advisable unless particle biogenesis is documented by a live imaging technique(6).

Other types of extracellular vesicles are the apoptotic bodies which have usually a diameter between 1-5μm. Formation of apoptotic bodies is exclusively linked to the latest stages of apoptosis where there is cellular shrinkage and nuclear fragmentation. Nuclear material, cell organelles and a permeable membrane are distinguishable characteristics of apoptotic bodies(9). In general, ectosomes are larger than exosomes (30-100nm) and smaller than apoptotic bodies(Figure 1). Additionally, the content may be different. For example, exosomes contain some membrane specific markers which are related with their formation process, such as lysosomal-associated membrane protein 1 and the membrane protein CD63. For microparticles, externalisation of the negatively charged phospholipid phosphatidylserine is the rule but for exosomes it is a rare structural condition. Also exosomes might contain cytosolic RNA but not like microparticles nuclear material(10). The above "rules" have exceptions to the degree that specific identification criteria based on size and/or markers seems to be causing more confusion than consensus(11).

In this review, we have included research articles related with extracellular vesicles which their diameter is between 100nm-1μm and they have at least one marker to describe their membrane biochemical composition. Furthermore, the cell(s) of origin are usually known to be related either with the biomarker or with the experimental process and the analysis method. In the vast majority of the literature these vesicles are called "microparticles" and thus, we kept that term.

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3. Biology

3.1 Inducers and mechanisms of formation

Potentially, any cell of an eukaryotic organism can produce microparticles(12). In the blood, the most common(70-90%) of the circulating microparticles are platelet derived microparticles. The rest of the blood containing microparticles are from endothelial, granulocyte, erythrocyte and smooth-muscle cells(13). Microparticles from epithelial, tumour cells, fibroblasts and other cellular origin have been also isolated(14,15).

Apart from the formation of the microparticles under normal circumstances, which is mainly linked with growth, differentiation and apoptosis(16), there are other non-physiological conditions that promote microparticle production. These conditions include hypoxia(17), shear stress(18), inflammation(19) and a variety of prothrombotic or proapoptotic factors(20)(Table 1). Usually, the first result after exposure of the cell to these factors, is an increase of Ca^{+2} influx(21)(Figure 2). High concentration of the intracellular Ca^{+2} induces molecular processes resulting in the release of the microparticles in the extracellular media(21).

The general assumption is that loss of the phospholipid asymmetrical set up of the plasma membrane, which is present during cellular relaxation, leads to the production of the microparticles(22). Externalisation of phosphatidylserine, a negative charged phospholipid, primarily located on the inner surface of the plasma membrane of the non-activated cell, results in the membrane asymmetry(23). Several phospholipid transporters regulate the inwards (flip) or outwards (flop) translocation of the plasma membrane lipids. An ATP-dependent “floppase” is responsible for the outwards translocation of the phosphatidylserine with simultaneous inhibition of flippase(s)(24). Non-specific, bidirectional lipid transporters, the “scramblases” (25) along with the formation of transient membrane pores constitute another pathway for the membrane remodelling(26).

The intracellular influx of Ca^{+2} is also involved in the shaping of the plasma membrane protrusions which results in the formation of microparticles(22). This process begins with degradation and reconfiguration of the cytoskeleton proteins(27). The proteolysis of specific part of the cytoskeleton network, by calpain activation, causes separation of the membrane

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protrusion from the parental cell as independent vesicle into the extracellular media(28). Another group of proteases, the capsases, is also associated with cytoskeleton ingredient lysis like talin, filamin, and gelsolin(29). Capsases are involved in the actin-myosin cytoskeletal network reorganisation by interacting with various Rho-kinases isoforms(30,31). Rho-kinases mediated microparticle shedding, with possible cellular nucleic acid redistribution, appears to be involved in apoptotic processes(32).

Phosphatidylserine exposure is commonly involved in microparticle formation from activated or apoptotic cells(33). However, there are less controlled situations where stress or injury induce cellular necrosis and loss of membrane integrity with production of microparticles(34). Also, there are populations of microparticles that are phosphatidylserine-(i.e., they do not bind Annexin-V), suggesting alternative formation processes(35). Further evidence of other ion channel involvement in the microparticle formation cascade, apart from Ca^{+2}, support the presence of unknown mechanisms associated with plasma membrane shedding(36).

(Table 1)

3.2 Structure and content

Microparticles contain a wide variety of biological molecules as part of their phospholipid membrane or within the cytosol that they enclose (Figure 3). These molecules are proteins (signal proteins, receptors, effector proteins), lipids and nucleic acids (38–40). Various techniques have been tried in order to characterize the components of the microparticles (41,42). Irrespective of the origin of microparticles, the plasma membrane is negatively charged due to translocation of phospholipids such as phosphatidylserine and phosphatidylcholine from internal to external surface(43,44). Other phospholipids of the membrane include lysophosphatidylcholine, sphingomyelin, lysophosphatidylethanolamine, phosphatidylethanolamine, lysophosphatidylserine, and phosphatidylinositol(45). It appears that the bi-lipid layer of the microparticles affects the attached protein activities and the general properties of the vesicles(46).

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The origin of the microparticles influences their composition. For example, platelet derived microparticles are enrich in various membrane proteins that are important in the coagulation process such us GPIb, GPII-IIIb, P-selectin, intergrins(47–49). Similarly, microparticles from endothelial cells carry characteristic endothelial proteins (vascular endothelium cadherin, E-selectin)(50) and leucocyte derived microparticles are enriched in metalloproteinases and other proteolytic enzymes(51) involved in inflammation process. Antigenic clusters of differentiation (CD31, CD105, etc) which derive directly from the parental cell, are present in the plasma membrane of the microparticles(52) (Table 2).

The stimuli that triggers the formation of the microparticles regulates the ratio and the composition of the expressed membrane proteins. For example, monocytes have been stimulated by various substances in vitro (lipopolysaccharide, soluble P-selectin chimera, phosphate-buffered saline) and the produced microparticles expressing different membrane proteins. Similar findings were reported for microparticles derived from other cellular lines such as T cells(53), endothelial cells(52) and leucocytes(54). However, all microparticles shared some common molecules(55).

The nucleic acids contained into the microparticles are usually result of apoptotic process(56). Different types of RNA (ribosomal, micro and messenger) and DNA are enclosed into membrane vesicles which are protected from nuclease exposure and might be activated into the target cells. RNA packaging is influenced by the variation of the stimuli that trigger microparticle formation(57). This selective translocation of nucleic acids contributes to intercellular communication(58,59).

(Table 2)

4. Functions related with cardiovascular physiology

4.1 Transfer of Biological information

Several biological functions of microparticles can be summarised with the title “factors of intercellular communication and information exchange”. In principle, there are 2 ways microparticles may contribute to intercellular signalling. The first is mediated by activation of receptors on the plasma membrane of the target cell by presentation of molecules which

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result in alteration of the cellular function. The second way of interaction is by direct transfer to the target cell bioactive components such as proteins, lipids and nucleic acids (Table 3). The target cell can utilise these molecules by affecting its biological function by activation of certain pathways or by phenotypic modification(48,72,73). Phenotypic modification is achieved usually by transferring membrane receptors to the recipient cell. These receptors interfere with stimuli that before transfer did not influence cellular activity at all or not by the same way(74).

Proteins can also be carriers of biological signal. Apart from membrane proteins, microparticles might have proteins in their cytosol in various forms. After incorporation of the microparticles into the target cell by phagocytosis, the proteomic load can be in an activated form or can be cleaved and activated by proteolytic enzymes into the target cell(75,76).

Reverse transcription polymerase chain reaction and microarray analysis demonstrated that microparticles carry a specific subset of messenger RNA or microRNA from the origin cell(76). By this manner, microparticles transfer to the target cell transcriptional information, analogous to the stimulating factor. The recipient cell will promote several processes, such as differentiation, proliferation and apoptosis by expressing different gene(77,78).

Lipids are not only components of the plasma membrane of the microparticles but actively determine the role of the ectosomes and their interaction with other cells(79). This function is mediated by the surface provided by microparticle membrane and from bioactive lipids such as arachidonic acid, cyclooxygenase 2 and prostacyclin(80,81).

(Table 3)

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4.2 Coagulation

The involvement of microparticles in the coagulation process was apparent from the time of their discovery(102). The strongest procoagulant activity is mainly related to the negatively charged, external surface of their plasma membrane due to the presence of

phosphatidylserine. The phosphatidylserine electrostatically attracts the positively charged segment of clotting proteins such as factors VII, IX and X, and prothrombin. The presence of γ-carboxyglutamic acid (GLA) domains creates the cationic features of these clotting factors(103)(Figure 4).

Additionally, tissue factor as plasma membrane protein of the microparticles appears to play key role in the coagulation process. Tissue factor is an integral protein of the coagulation cascade and acts as a receptor of the FVII/VIIa complex, which activates both factors IX and X to initiate thrombin formation. Tissue factor positive microparticles may derive from monocytes, neutrophils, endothelial cells and platelets as response to various pathological conditions(104). P-selectin, a cell adhesion receptor, interacts with tissue factor positive microparticles, through P-selectin glycoprotein ligand 1 (PSGL-1) on monocytes and causes further tissue factor positive microparticles generation which carry PSGL-1. These microparticles bind to activated platelets on the site of vascular injury and contribute further to thrombus expansion(105).

Finally, another possible mechanism of microparticles prothrombotic actions is inhibition of the fibrinolytic process. Expression of proteins on the plasma membrane of microparticles like plasminogen activator inhibitor-1 and protein S, leads to amplification of thrombogenesis by suppression of fibrinolysis(106,107).

4.3 Inflammation and immune regulation

Part of intercellular communication features of microparticles has been related with the immune regulation. Immune and non-immune cells may produce microparticles which carry antigens. In this context, microparticles can influence immune responses to foreign(108) or self-antigens(109). All immune cell types under certain stimuli can generate microparticles but the most effective, with regard to the regulation of immune response, are the "professional" antigen-presenting cells, such as dendritic cells, macrophages, and B cells(110). This is achieved by binding the antigen to the cell surface or by phagocytosis(111,112).

Microparticles have pro-inflammatory effects mainly by inducing the production of cytokines and chemokines and by the activation of inflammatory cells(37)(Table 4). This recruitment of

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inflammatory mediators can be done without the presence of micro-organisms(113). Administration of endothelial microparticles to rats is associated with release of pro-inflammatory cytokines IL-1β and TNF-α, acute lung injury and histological damage as evidence from the neutrophil infiltration into the perivascular space(114).

In vitro studies reported release of cytokines IL-6 and monocyte chemotactic protein from endothelial cells after stimulation by neutrophil microparticles(115). Furthermore, pro-inflammatory cytokine secretion, such as IL-8, TNF-a and IL-1β, have been described from other cellular cultures after exposure to microparticles(43,116).

In addition to chemotactic factors, microparticles are involved in the production of specific cellular membrane proteins which promote adhesion of inflammatory cells to endothelium. Examples are the intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin(95,117). Bioactive lipids produced by platelet derived microparticles, like thromboxane A2 and cyclooxygenase, may act as mediators of inflammation. The target tissue is usually the endothelium(79).

Cases have been described where microparticles from polymorphonuclear leukocytes antagonise parallel pro-inflammatory stimuli by releasing cytokines like transforming growth factor beta 1. Polymorphonuclear derived microparticles also contain annexin 1, a protein with anti-inflammatory properties. Annexin-1 and transforming growth factor beta 1 inhibit macrophages. This action usually occurs during the early stages of the inflammatory process(118,119). Microparticles from monocytes were found to induce macrophages and monocytes expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) protein with anti-inflammatory action. In the same study, monocyte microparticles promoted inflammatory [reactive oxygen species (ROS), cytokines] or anti-inflammatory (PPAR-γ) molecules in dose dependant manner(120). Another mechanism which associated with polymorphonuclear derived microparticles mediated inflammatory process is activation of complement. Purified complement proteins like C1q from serum were found to be carried by polymorphonuclear derived microparticles(51).

(Table 4)

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4.4 Angiogenesis

The platelet derived microparticles were the first group of microvesicles demonstrated angiogenetic properties in vitro. Platelets are known carriers of neovascularisation factors. Bioactive lipids from platelet derived microparticles (Table 5) are the main inducers of proliferation and tube formation in human umbilical vein endothelial cells(90,121). Experiments in rat models reported angiogenesis in ischaemic myocardium after injection of platelet derived microparticles. The process was facilitated by vascular endothelial growth factor, basic fibroblast growth factor and inhibition of platelet factor-4(91). Also, tissue factor positive microparticles can induce endothelial cell proliferation through a beta 1-integrin and extracellular signal regulated kinase activation(122).

Another microparticle related neovascularisation mechanism is possibly associated with the morphogen Sonic Hedgehog pathway. T-cell derived microparticles, harbouring the Sonic Hedgehog antigen, promote in vitro and in vivo formation of new vascular network by regulating the nitric oxide pathway and stimulate genes coding expression of adhesion molecules and proangiogenic factors(123,124).

Endothelial derived microparticles have also angiogenetic properties. Plasmin formation on the surface of the endothelial derived microparticles might activate proteolytic pathways and generation of factors which promote tube formation from endothelial cells(125). In addition, matrix metalloproteinases carried by endothelial derived microparticles contribute to matrix-degrading proteolytic activity necessary for the angiogenetic events(126). Neovascularization programming by endothelial derived microparticles appears to be conducted in relation with direct transfer of mRNA to target endothelial cells which codifies the formation of capillary-like structures(38). In vivo demonstration of the angiogenetic features of microparticles was reported by Leroyer et al(127). Microparticles derived from ischaemic muscle injected into ischemic legs in a rat model resulted in enhanced neovascularization.

Adipose cell derived microparticles from rats was also found to be carriers of angiogenetic molecules, such as leptin, fibroblast growth factor alpha (FGFa) and TNFa and in collaboration with tissue matrix metalloprotease (MMP)-2 and MMP-9 may promote neovascularization(128).

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A combined signal transmission from microparticles that regulates the functions of angiogenesis, apoptosis, differentiation and migration might contribute to tissue regeneration and remodelling(129). After permanent middle cerebral artery occlusion in rats, administration of platelet derived microparticles increased neurogenetic and angiogenetic activity, followed by behavioural improvement but no changes in infracted volumes(130).

The role of microparticles in angiogenesis is not always promotive but may be inhibitory. There are reports about prevention of neovascularization by microparticles. For example, human umbilical vein endothelial cells vascular network proliferation was inhibited by the presence of endothelial derived microparticles(131). Similarly, lymphocyte-derived microparticles were found to cause overexpression of the CD36 anti-angiogenic receptor while significantly downregulated protein levels related with angiogenesis(132). The generation of reactive oxygen species such as hyperoxide is likely to be involved in the inhibitory process. The balance between inhibition and promotion of neovascularization, for different types of microparticles, appears to be affected by their concentration along with other potential unknown factors (126,132,133).

(Table 5)

4.5 Regulation of vascular tone

Several studies have established a link between endothelial activity, expressed by modification of vascular tone and microparticles. Microparticles may affect the regulation of nitric oxide synthetase resulting in impaired production of nitric oxide in vivo(108,134). Endothelial derived microparticle may also impair vasorelaxation. This was demonstrated in patients with end stage renal failure and type 2 diabetes, where different sonographic indices of arterial function have been assessed(61,135). Furthermore, endothelial relaxation was impaired in aortic rings after exposure to endothelial derived microparticles from patients with recent myocardial infarction, in contrast with endothelial derived microparticles from non-ischaemic patients(136).

Lymphocyte derived microparticles also affect the nitric oxide synthetase activity(137,138). The mechanism driven the synthetase downregulation is related with the phosphorylation of

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the extracellular signal–regulated kinase 1/2 via phosphatidylinositol-3-kinase and nuclear factor κ-light-chain-enhancer of activated B cell pathways(137). Additionally, lymphocyte derived microparticles may induce endothelial overexpression of the integral membrane protein caveolin-1 which inhibits the nitric oxide synthetase(138).

Endothelial and platelet derived microparticles are carriers of endothelial nitric oxide synthase and in patients with cardiovascular risk factors the isolated microparticles found to have significant less levels of the synthase compared with healthy subjects(139). Platelet derived microparticles can also influence the vascular tone as they are involved in the production of vasoactive molecules such as prostacyclin (vasodilator)(80) or thromboxane (vasoconstrictor) (140). In experimental models, microparticles can modify cyclo-oxygenase metabolites levels through the Fas antigen and its natural ligand FasL pathway(141).

4.6 Apoptosis

Microparticles production can be the result from an apoptotic process along with the formation of apoptotic bodies. Additionally, microparticles can also induce programmed cellular death of remote cells(142,143). Anti-apoptotic stimulation showed a reduction in the cell "blebbing" and microparticle formation in Human tonsil germinal center B cells in vitro. B cell blebs appear to have chemo-attractive properties to macrophages which carry out the apoptotic cell removal(144). Endothelial derived microparticles can initiate apoptosis in angiogenic cells. The rich in arachidonic acid microparticles are phagocytosed by the angiogenic cells and signalise apoptosis. This action, as other functional roles of the microparticles, is concentration dependant(145). Apoptosis mediated by the lipid synthesis of the microparticle is also possible, even without involvement of phagocytosis. PtdIns(3,5)BP is a specific inhibitor of the acid sphingomyelinase which can inhibit the apoptosis pathway via upregulation of the capsase-8. Inhibition of the extracellular signal regulated kinase 1 prevents the apoptosis of macrophages in vitro. Extracellular signal regulated kinase 1 as microparticle membrane protein activate target cell membrane phospholipases and contributes to formation of arachidonic acid from phospholipids(146). Capsase-3 protein is also involved in apoptosis(147) and has been identified as membrane protein in platelet derived microparticles and endothelial derived microparticles(148,149).

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The signal for programmed cellular death to remote cells can be transmitted by microparticles through the Fas antigen and its natural ligand FasL. This mechanism was demonstrated in human tumour cells in vitro(150). Additionally, tumour derived microparticles contain matrix metalloproteinases responsible for matrix degradation but also adhesion molecules and receptors like the CX3CL1/fractalkine system which regulates migration and apoptosis(151).

4.7 Oxidative stress

Oxidative stress is caused when there is an imbalance between production of reactive oxygen species and the antioxidant defence mechanisms(152). Controlled production of reactive oxygen species is important as contributes to cell growth, adhesion, differentiation, and apoptosis(153). Brodsky et al(134) reported an active role of endothelial derived microparticles in the formation of superoxide. Also, the p22(phox) subunit of NADPH oxidase has been detected in endothelial derived microparticles. Also, microparticles from other cellular origin, such as lymphocytes and monocytes, may lead to the production of reactive oxygen species(132,154). Monocyte derived microparticles can induce nitrosative stress in endothelial cells in vitro. This occurs by increasing the nitration of several proteins in endothelial cells after regulating calveolin-1 expression or activation of phosphatidylinositide-3 kinase and other extracellular signal–regulated kinases(155).

5. Microparticles and cardiovascular risk factors

5.1 Essential Hypertension

Mechanisms, such as excessive amounts of reactive oxygen species and oxidative stress, which are linked with microparticles, have been described to be involved in the pathogenesis of endothelial dysfunction due to hypertension(156,157).

The Renin-angiotensin system in known to have a fundamental role in the regulation of arterial hypertension(158). Angiotensin II, a potent vasoconstrictive hormone can induce the formation of microparticles from monocytes in vitro. The derived microparticles expressed tissue factor on their membrane and demonstrated procoagulant activity(159). Procoagulant features of microparticles reported by Preston et al(160) in patients with severe hypertension.

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The hypertensive cohort had increased levels of platelet and endothelial derived microparticles with strong positive correlation between two types circulating microparticles (CD31+ endothelial derived microparticles and CD62P + platelet derived microparticles) and absolute levels of systolic and diastolic blood pressure. Tissue factor expression on endothelial derived microparticle and platelet factor 3 on platelet derived microparticles might explain the procoagulant features of microparticles and thrombogenity of hypertension.

High levels of circulating endothelial derived microparticles with synchronous reduction of endothelial progenitor cells (EPC) as expressed by increased ratio of endothelial derived microparticles/EPC were detected in hypertensive patients with reduced glomerular filtration rate and microalbuminuria. The endothelial progenitor cells are considered to promote endothelial integrity and vascular repair. On the other hand, the CD31/annexin V+ apoptotic microparticles were related with atherosclerotic disease and further deterioration of the renal function(161,162).

5.2 Diabetes mellitus

Endothelial derived microparticles(CD62E+) are higher in a pre-diabetic cohort along with elevated biomarkers of endothelial dysfunction(163)(Table 6), suggesting an involvement of microvesicles in the pathogenesis of the disease. In patients with established diabetes, the absolute number of microparticles was also found to be elevated. Kurtzman et al(164) reported increased number of several microparticle phenotypes in diabetics compared with healthy controls(164). Similar findings were demonstrated by a metanalysis of 48 studies involving 2,460 patients with Type 2 diabetes(165).

Different types of microparticles, such as endothelial, platelet, erythrocyte and monocyte derived microparticles have also been found to be elevated in diabetic populations(61,166–168). Monocyte, endothelial and platelet derived microparticles are significantly higher in diabetic patients with related vascular complications such as nephropathy, retinopathy or neuropathy compared with diabetic patients without complications(63,167,169,170).

Patients with type 1 diabetes mellitus have not only higher but also different types of circulating microparticles compared with patients with type 2 diabetes mellitus and healthy people(65). Platelet, endothelial and apoptotic cell (annexin V+) derived microparticles were

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significantly elevated in type 1 diabetes. The different microparticle phenotypes between the two conditions reflect differences in their functional and particularly their procoagulant properties. For type 2 diabetes patients, these microparticles have limited procoagulant action but for type 1 diabetes their prothrombotic properties were positively correlated with the glycaemic control [HbA1c](65). The relation between glycaemic control and microparticles have been demonstrated in a study of overweight subjects with type 2 diabetes. The levels of the circulating microparticles have been reduced after bariatric surgery with synchronous normalization of glycaemic control (69).

The pathophysiology of hypercoagulopathy in diabetes has been linked with the presence of microparticles(65,171,172). Abnormal production of reactive oxygen species mediated by microparticles along with inappropriate protein expression on the microparticle membrane which relate to coagulation and immune pathways have been demonstrated in vitro(172). Tissue factor antigens on the membrane of circulating microparticles in patients with type 2 diabetes was reported by Cimmino et al(171) and is likely to be involved in the prothrombotic activity along with other athero-imflammatory processes observed in diabetic populations. Microparticle coagulability (expressed by the density of membrane tissue factor and membrane tissue factor pathway inhibitor ratio) was found to be high in diabetic patients with severe foot ulcers and manifestations of coronary artery disease(173). Similar findings regarding hypercoagulability of plasma microparticles in diabetic patients reported by Tripodi et al(174) as measured and correlated by conventional coagulation tests such us antithrombin and protein C activity and levels of factors II and VIII.

Diabetic vascular complications are associated with vascular inflammation and endothelial dysfunction(175). Endocytosis of platelet derived microparticles from endothelial cells in vitro induced expression of von Willebrand factor on the plasma membrane of the endothelial cells, which promoted adhesion of platelets and excessive production of reactive oxygen species leading to inflammation(67). Microparticles mediated reactive oxygen species production in diabetics is involved in downregulation of NO activity affecting the vascular tone and contribute to leukocytes chemotaxis to endothelium by expression of surface antigens(176,177). In clinical studies, type 2 diabetes, is associated with high levels of endothelial/apoptotic cell derived microparticles and asymptomatic coronary atherosclerotic disease(178).

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Microparticles have been demonstrated to be involved in impaired neovascularization process in diabetic populations. Incubation of human umbilical vein endothelial cells with extracellular microvesicles from patients with diabetic foot or diabetic retinopathy induced the formation of tube networks, suggesting an important role of the vesicles in the process of angiogenesis(173). Tissue factor positive microparticles in well controlled diabetic patients are not always involved in coagulation process and potentially have a role in signal transmission, including angiogenesis(70,179). MiR-126, a type of RNA, which is contained in microparticles was reported to play important role in endothelial integrity and angiogenesis(180). Reduced expression of miR-126 in endothelial derived microparticles from diabetic patients might contribute to endothelial injury, abnormal vascular remodelling and impaired angiogenesis(181,182).

Various medications were investigated regarding their effects in the levels of circulating microparticles in diabetes. Apart from the antidiabetic drugs, anti-hypertensives, statins and anti-platelets have been demonstrated to decrease the microparticles in various populations with diabetes (Table 7) (183).

(Table 6)

(Table 7)

5.3 Smoking

Smokers have significantly higher levels of plasma tissue factor concentrations(205). Human monocytes and macrophages produce microparticles and demonstrated apoptotic activity in vitro, after exposure to tobacco smoking extract. These microparticles were found to be tissue factor positive, reflecting their procoagulant properties(206).

Smokers with normal spirometry but reduced diffusing capacity of the lung for carbon monoxide have also elevated levels of endothelial derived microparticles, likely derived from apoptotic endothelial capillary cells(207). Another mechanism which appears to be induced by tobacco smoke inhalation is microparticle gelatinolytic and collagenolytic activities. After exposure to tobacco smoking extract in vitro, human macrophages produce microparticles with transmembrane matrix metalloproteinase 14 (MMP14). These microparticles may

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mediate extracellular matrix destruction leading to inflammation, atherosclerotic plaque vulnerability and tissue necrosis(208). Elevation of endothelial derived microparticles was also observed in passive smokers along with endothelial dysfunction, as assessed by flow-mediated dilation using ultrasound. In the same study, the endothelial progenitor chemotaxis toward vascular endothelial growth factor was impaired resulting in reduction of nitric oxide production and endothelial dysfunction(209).

5.4 Dyslipidaemias

Endothelial derived microparticles were found to be elevated in patients with uncomplicated type 2 diabetes mellitus after consumption of high-fat meals. This elevation was correlated with other dysmetabolic changes such as high levels of glucose, insulin, and triglycerides and low levels of high density lipoprotein(210). Hypercholesterolaemia along with endothelial derived microparticles has inhibitory activity in cardiac angiogenetic mechanisms through imbalance of the endothelial nitric oxide synthetase regulation(211). Hypercholesterolaemic conditions may induced endothelial damage associated with microparticles but there is evidence that can also promote generation of prothrombotic vesicles. Aggregated low density lipoprotein was found to induce release of tissue factor positive microparticles from human vascular smooth muscle cells(212). Similarly, monocytes enriched by cholesterol in vitro, appear to expose phosphatidylserine on their cellular membrane along with induction of apoptosis and release increased levels of tissue factor positive microparticles(213). Additionally, phosphatidylserine expression mediated by oxidative low density lipoprotein in diabetic population was associated with elevated levels of platelet derived microparticles(214).

The relation between the endothelial protective role of high density lipoprotein and microparticles has been investigated(43,215). High density lipoprotein was reported to inhibit the binding of the T cell derived microparticles to monocytes and sequelae monocyte activation. Furthermore, high density lipoprotein partially inhibited production of pro-inflammatory cytokines from monocytes .

In several studies which recruited patients with type 2 diabetes and hyperlipidaemias (Table 5) there was a reduction of the circulating microparticles after treatment with statins. For example, in patients with type 1 diabetes mellitus and hyperlipidaemia, treatment with

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atorvastatin reduced gpIIIa, P-selectin- and tissue factor-containing microparticles(197). For patients with type 2 diabetes and hyperlipidaemia, treatment with pravastatin for 8 weeks did not alter significantly the blood cholesterol concentrations but reduced the gpIIb/IIIa membrane receptor in the circulating platelet derived microparticles. GpIIb/IIIa is an important receptor for fibrinogen involved in thrombus formation. Downregulation of this receptor which is possibly induced by changes to platelets and microparticles lipids membrane composition might contribute to less thrombotic risk(71). Fluvastatin reduced microparticles in vitro from cultured human coronary artery endothelial cells by inhibition of the Rho kinase pathway which is responsible for alteration of cytoskeleton(216).

High triglycerides levels is a component of metabolic syndrome among with hyperinsulineamia, hypertension and low high-density lipoprotein cholesterol levels(217). Elevation of endothelial(218), platelet(219) and leukocytes derived microparticles(220) in patients with metabolic syndrome contribute to vascular inflammation and hypercoagulant status which promote atherosclerosis and thrombosis(141). In an observational study(221) participating patients with metabolic syndrome, dyslipidaemia was associated with higher levels of endothelial derived microparticle (CD144+) and erythrocyte microparticle (CD235a+) compared with healthy control group. Obesity influenced the levels of platelet (GpIIb/IIIa+) and endothelial derived microparticles and hypertension only the endothelial derived microparticles. Levels of AnnexinV+ microparticles were affected by each of the different components of metabolic syndrome.

6. Microparticles and cardiovascular diseases

6.1 Atherosclerosis

Various mechanisms contributing to initiation, progression and clinical manifestation of atherosclerotic disease are associated with the presence and formation of microparticles (Figure 5). The disruption of the normal levels and composition of the microparticles might represent one of the initial steps of the atherosclerotic disease. The link between apoptosis and microparticle production is well-established(142). Reduced laminar shear stress is also reported as a signal for endothelial apoptosis(222) which potentially contributes to microparticle production and imbalance of the normal endothelial features(223).

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Endothelial permeability occurs during the first phase of the atherosclerotic process(224). Findings suggest a link between endothelial permeability and microparticles. Injection of endothelial derived microparticles in rats significantly increases the pulmonary capillary permeability and causes acute lung injury. This action is likely mediated through inhibition of nitric oxide generation and sequelae impaired vasodilation(225). Abnormal endothelial homeostasis related with nitric oxide production have been reported with endothelial derived microparticles(136) and T lymphocyte-derived microparticles in vitro(138). Another mechanism, mediated by CD54, might play a role in atherogenesis. It was described in patients with multiple sclerosis where endothelial derived microparticle CD54+ induce inflammation and increase migration of monocytes through the endothelium(226). Additionally, platelet derived microparticles can affect the endothelial cell barrier integrity, in a manner related with their size and protein composition(227).

Chemo-attraction of leukocytes to the inflamed endothelial segment is essential for the progression of atherosclerosis(228). Microparticles from different cellular origins may trigger production of pro-inflammatory cytokines from the endothelium, such as IL-6 and IL-8, which attract and activate leukocytes(95,229). Another suggested mechanism which contributes to the progression of the atheroma is linked to microparticles-induced expression of adhesion molecules on the endothelial cells. An example is platelet derived microparticles mediated upregulation of intercellular adhesion molecule-1 on the endothelial cell membrane(95,230). Plaque microparticles isolated from endarterectomy specimens could transfer ICAM-1 to endothelium(231). Also microparticles induce integrin expression on the surface of the leukocytes, such as CD11a and CD11b, which interact with intercellular adhesion molecule-1(95). Chemokines delivered from microparticles to inflamed or atherosclerotic endothelium promote further leukocyte recruitment. Mause et al described a platelet derived microparticle-associated delivery of the chemokine RANTES (regulated on activation, normal T cell expressed and secreted) to human microvascular endothelial cells which promotes monocyte adhesion(89).

Microparticles concentrations are 200 times higher in atherosclerotic plaques than in blood(232). Microparticles derived from leukocytes have the higher levels in plaques; 29% found to be from macrophages, 15% from lymphocytes and 8% from neutrophils. Other significant populations of microparticles concentration delivered from erythrocytes (27%),

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smooth muscle (13 %) and endothelial cells (8%)(232). Microparticle origin in atherosclerotic plaques was not found to be affected by symptoms of ischaemia(232). All plaque microparticles, regardless their origin, possess pro-coagulant activity as they express tissue factor on their external plasma membrane surface(233).

Furthermore, atherosclerotic plaques microparticles was described that contain immunoglobulins. The immunoglobulins they expressed were found to be different from the plasma circulating microparticles(234). Co-labelling of IgG and CD14 demonstrated that the vast majority of microparticles (93±7%) containing IgG were CD14+, revealing their macrophage origin(234). High macrophage infiltration was observed also in raptured atherosclerotic lesions with concurrent macrophage apoptosis(235). Microparticles are involved in macrophage apoptosis but is unknown if this mechanism contributes to rapture or characterise vulnerability of the fibrous cap of the atheromatous plaques(236). Additionally, as macrophages have been involved in the clearance of microparticles, defective phagocytosis due to increased macrophage apoptosis may lead to accumulation of microparticles(237–239). A point towards this hypothesis is the acceleration of atherosclerotic lesions in mice which lack lactadherin activity(240). Lactadherin is essential protein for the removal of the microparticles(241).

Atherosclerosis is a complex immune-inflammatory disease which several type of cells are involved, including lymphocytes (T, B, Natural killer T), dendritic cells, and mast cells(242). In vitro, endothelial derived microparticles induced dendritic cell maturation and secretion of pro-inflammatory cytokines, contributing to CD4 T cells activation and proliferation(243). In the same study, microparticles from activated T cells or platelets failed to stimulate dendritic cell maturation(243). Polymorphonuclear neutrophil-derived microparticles were reported to interact with human monocyte-derived dendritic cells and to promote morphologic changes which reduce monocyte phagocytic activity and increase cytokines excretion(244). Additionally, microparticles from activated dendritic cells can interfere with resting dendritic cells and transfer antigens to them(245). These antigens can be presented to lymphocytes leading to their activation and proliferation(245). Microparticles from T cells may also stimulate mast cells. This action can take place by transfer of membrane biomolecules via microparticles instead of cellular contact(246).

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Smooth muscle cell proliferation and migration from the media to intima is essential for the formation of the atheroma(228). Platelet derived microparticles were found to have mitogenic effect on smooth muscle cell in vitro, with no chemotactic contribution(247). The mitogenic effect increased synergically if platelet derived microparticles were combined with serotonin or thromboxane A2(248). The chemotaxis for smooth muscle cell migration is strongly mediated by tissue factor receptors(249,250). Microparticles isolated from atherosclerotic plaques express tissue factor in their surface(233) and might act as a chemo-attractive factor for smooth muscle cell migration and proliferation.

The intraplaque neovessel formation due to hypoxia and inflammation influences the stability of the atherosclerotic lesion(251,252). Microparticles might play a significant role in the neovascularization. They can carry proteolytic enzymes on their membrane and they have ability to induce the production of metalloproteases from other cells, so the endothelial tissue would be able to penetrate the surrounding interstitial matrix(253–255). Furthermore, plaque microparticles mainly of macrophage origin can induce endothelial cell proliferation in vivo(256). On the contrary, in this study circulating microparticles were unable to induce endothelial cell proliferation(256). CD40/CD40 ligand system appears to play an important role in the microparticles endothelial cell interaction(256). Patients with symptoms of cardiac ischaemia expressed more CD40L than asymptomatic patients and their microparticles were more potent endothelial proliferation inducers in vitro(256).

Studies of patients with early atherosclerosis and chronic coronary artery disease showed increased levels of CD144+/CD31+ endothelial derived microparticles expressing T-cadherin compared with healthy volunteers. T-cadherin was found to reflect endothelial dysfunction as measured by reactive hyperaemia following brief peripheral flow occlusion(257). Plasma levels of CD144+/ CD42b- endothelial derived microparticles predicted the presence of coronary artery disease in asymptomatic diabetic patients (258).

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6.1.1 Acute coronary syndromes

In the setting of acute coronary syndromes, the most studied microparticles are platelet derived microparticles and endothelial derived microparticles. Observational studies showed increased levels of CD146+ and CD31+ endothelial derived microparticles (Table 8) in patients with acute coronary syndrome compared to patients with stable angina or with no

coronary artery disease(259,260). Acute coronary syndromes are associated with raised thrombotic activity. Morel et al described that patients with ST elevation myocardial infarction and unstable angina had higher levels of procoagulant microparticles compared with patients with stable angina. The principal population of procoagulant circulating microparticles were platelet derived microparticles GPIb+ and endothelial derived microparticles CD31+(261). The majority of endothelial derived microparticles expressed the pro-atherogenic adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1)(262).

Revascularization affects the levels of the circulating microparticles as reduces the endothelial injury. In a cross-sectional study, a significant reduction in Annexin V-binding and endothelial microparticles observed after primary percutaneous coronary intervention (PCI) in ST elevation myocardial infarction patients, compared to patients with stable coronary artery disease or non- ST elevation myocardial infarction before PCI(263). Zhou et al(264) investigated the levels of three groups of microparticles (endothelial derived microparticles CD144+, platelet derived microparticles CD41+ and leukocyte-derived microparticles CD45+) during the acute phase of ST elevation myocardial infarction /primary PCI and 48 hours later. Platelet derived microparticles increased immediately post PCI and reached the maximum levels 48 hours later. Endothelial derived microparticles and CD45+ microparticles decreased immediately post PCI and gradually increased up to 48 hours later(264). Abciximab, an GPIIb-IIIa antagonist, in combination with primary coronary angioplasty reduces the level of platelet derived microparticles compared with patients that had only percutaneous angioplasty(261). Failure of revascularisation strategy, such as thrombolysis, induced higher levels of procoagulant microparticles (tissue factor + microparticles)(265).

Differences were also detected in the levels of circulating annexin V+ and tissue factor+ microparticles as regard the vascular level of origin. Microparticles were elevated in the culprit artery compared with the peripheral blood in patients with ST elevation myocardial infarction after primary percutaneous coronary intervention, suggesting local vascular damage(266,267).

Biasucci et al(268) demonstrated a relation between high-sensitivity C-reactive protein (hs-CRP) endothelial and platelet derived microparticles levels in patients with stable coronary artery disease and acute coronary syndrome. The annexin V+ microparticles were related to

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the troponin T levels and the degree of myocardial injury. No significant differences were detected regarding type of acute coronary syndrome (Non ST elevation myocardial infarction vs ST elevation myocardial infarction) and the levels of circulating microparticles(268). Endothelial derived microparticles and platelet derived microparticles were also found to be related with the extension of the MI(269).

(Table 8)

6.1.2 Peripheral vascular disease and ischaemic stroke

Endothelial derived microparticles were found to be elevated in patients with peripheral arterial disease and particularly microparticles expressing the monomeric CRP molecule on their membrane, suggesting the inflammatory nature of the condition(271). High levels of leukocyte derived microparticles (CD11a+) were also found in patients with non-symptomatic atherosclerotic disease demonstrated by ultrasound examination of carotid, abdominal aorta, and femoral arteries(272). Leukocyte (CD11a+) along with endothelial derived microparticles (CD105+) observed to be associated with higher carotid intima-media thickness in patients before atherosclerotic disease is evident(273). Platelet derived microparticles (CD63+) were also raised in patients with peripheral arterial disease with or without myocardial infraction(274) and after bypass grafting, reflecting the thrombotic nature of the disease. Certain cytokines such as IL-6, G-CSF and thrombopoietin were also detected to be high in patients with peripheral arterial disease and may related with microparticle formation from platelets(275).

Patients with recent ischaemic stroke were found to have higher levels of CD62E+ endothelial derived microparticles. More severe strokes, classified by National Institute of Health Stroke Scale score, were associated with higher CD62E+ endothelial derived microparticle levels, reflecting the severity of the endothelial damage and the degree of endothelial activation. From the same study, patients without stroke but with significant risk factors for atherogenesis and extracranial arterial disease had higher CD62E+ endothelial derived microparticle levels, in contrast to patients with intracranial arterial stenosis where the CD31+/CD42b- and CD31+/Annexin V+ endothelial derived microparticle subpopulation levels were raised(276). Simak et al(277) investigated the levels of endothelial derived microparticles in acute stroke patients using flow cytometry. Endoglin-positive endothelial

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derived microparticles (CD105+/CD41a-/CD45-), endothelial derived microparticles expressing VE-cadherin and endoglin(CD105+/CD144+), phosphatidylserine(CD105+/phosphatidylserine+/CD41a-) and Intercellular Adhesion Molecule-1(CD105+/CD54+/CD45-) were analysed. Only phosphatidylserine+ endothelial derived microparticles were significantly higher in the acute stroke group compared with the control. All the endothelial derived microparticles subtypes were elevated in patients suffering moderate to severe stroke (according to National Institutes of Health Stroke Scale). Significantly elevated Endogline and Intercellular Adhesion Molecule-1 positive endothelial derived microparticles on admission were associated with worse prognosis. Apart from endothelial derived microparticles, patients with acute ischaemic stroke were found to have increased levels of platelet derived microparticles (GpIIIa+) during the acute phase and up to 6 months later, compared with healthy controls(278), suggesting that thrombotic tendency might last more than the acute phase of the infarct.

6.2 Heart failure

For patients with non-ST elevation myocardial infarction, elevated endothelial derived microparticles and monocyte derived microparticles were associated with higher readmission rates from heart failure (Table 9)(263). Different factors may affect the levels and the origin of microparticles in heart failure patients. Endothelial derived microparticles(CD31+/Annexin V+) were higher in patients with 3 vessel coronary artery disease and Heart failure with reduced ejection fraction compared with patients with same degree of coronary artery disease but preserved Left Ventricular systolic function(279). The same type of microparticles were higher in patients with heart failure with reduced left ventricular ejection fraction and increased Body Mass Index (BMI>25kg/m^2) compared with other patients with lower BMI(280). Apoptotic annexin V+ microparticles were found to be elevated in heart failure patients with worse functional status (dyspnoea class III-IV of New York Heart Association scale)(281).

Subjects with heart failure and preserved left ventricular ejection fraction were found to have lower ratio of CD31+/annexin V+ endothelial derived microparticles to Endothelial progenitor cells (as expressed by CD14+/CD309+ and CD14+/CD309+/Tie-2+) in comparison with Heart failure with reduced ejection fraction patients. That ratio in

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combination with pro-BNP levels was demonstrated to have good discriminatory value between heart failure with reduced and preserved ejection fraction(62).

Few studies were conducted to assess the differences of various microparticles levels among patients with end stage heart failure requiring left ventricular assisting devices or heart transplantation. From an observational study(282), heart transplant patients were compared with heart failure patients and healthy controls regarding the levels of endothelial derived microparticles (CD62 E+ and CD31+). Heart failure patients had higher numbers of CD62+ endothelial derived microparticles compared with healthy and post-transplant patients. Apoptotic microparticles, based by the ratio of CD62E/CD31 (apoptosis=low ratio), were higher in transplant patients. More microparticle populations investigated in a study that enrolled heart failure patients, patients with left ventricular assisting devices and patients post heart transplant. Left ventricular assisting devices were associated with elevated levels of all microparticles types suggesting erythrocyte destruction and endothelial activation. In patients with heart transplant post left ventricular assisting devices, all microparticles levels were decreased(68). The endothelial damage, as expressed with phosphatidylserine+ microparticles, 3 months post left ventricular assisting device implantation, demonstrated to be lower compared to pre-implant period in heart failure patients, regardless the aetiology of heart failure(283).

Patients with congestive heart failure and metabolic syndrome was demonstrated to have higher levels of CD31+/Annexin V+ endothelial derived microparticles in addition with lower levels of CD62E+ endothelial derived microparticles compared with healthy subjects. The ratio of CD62E+ to CD31+/Annexin V+ endothelial derived microparticles was significantly lower among the patients with heart failure and metabolic syndrome in contrast to patients with metabolic syndrome but without heart failure and healthy subjects(66).

(Table 9)

6.3 Atrial Fibrillation

Patients with atrial fibrillation have increased risk of ischaemic stroke and were found to have higher levels of platelet derived microparticles (CD42b+/CD61+) in contrast with healthy subjects. There was no difference in the levels of circulating platelet derived

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microparticles between patients with permanent or paroxysmal atrial fibrillation or between patients on treatment with aspirin or warfarin. In the same study there were no significant differences in platelet derived microparticles for patients in atrial fibrillation and patients with established coronary artery disease and sinus rhythm(285). In another observational study, Annexin V+ microparticle levels were higher in atrial fibrillation patients compare with healthy controls and with patients with sinus rhythm but cardiovascular risk factors (disease control). On the contrary, platelet derived microparticles (anti-glycoprotein Ib+) and endothelial derived microparticles (CD31+) were similar in patients with AF and disease control group but higher compared with healthy control subjects(286).

In patients with chronic AF due to mitral stenosis CD41+ platelet derived microparticles levels were higher compared to healthy controls and there was a significant direct relationship between the mitral valve area and the levels of circulating platelet derived microparticles(287), suggesting higher risk of thromboembolic events with increasing severity of mitral stenosis.

Induction of AF during electrophysiology studies increased the P-selectin+ microparticles compared with chronic AF and control patients which might reflect different procoagulant mechanism between chronic and paroxysmal AF(288).

6.4 Pulmonary Hypertension

Diehl et al(289) reported increased levels platelet (CD31+/CD61+), Leukocyte (CD11b+) and endothelial derived microparticles(CD62E+) in pulmonary hypertensive patients compared with healthy subjects, suggesting that the mechanisms which are involved in the progression of the disease are associated with platelet activation, inflammation and endothelial dysfunction(289). In another study(290), several types of microparticles [platelet (CD31+/CD41+), endothelial(CD62E +, CD144+, CD31+/ CD41-), leukocyte (CD45+) and apoptotic (annexin V +) microparticles] were analysed from patients with precapillary pulmonary hypertension before any treatment with endothelium-active vasodilator therapy. Endothelial and leukocytes derived microparticles levels were higher among pulmonary hypertension patients compared to healthy control group. CD31+ and CD144+ microparticles levels were strongly associated with the haemodynamic severity of the disease.

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Results from an observational study(291) with paediatric patients and Eisenmenger syndrome suggested that CD144+ endothelial derived microparticles along with the thickness of pulmonary artery intima media and pulmonary stiffness can be used as non-invasive alternative tests to monitor the progression of the disease. Lin et al(292) also reported elevated endothelial derived microparticles (CD31+/ CD42b-) in adult patients with pulmonary hypertension secondary to atrial or ventricular septal defect.

A possible link between endothelial derived microparticles and increased phosphorylation of the P38 mitogen-activated protein kinases, was demonstrated in a rat model, which can induce inflammatory process along with impaired function of endothelial NO synthetase. Endothelial derived microparticles (endoglin+) from rats with advanced pulmonary hypertension can induce expression of Intercellular Adhesion Molecule-1 in pulmonary artery endothelial cells and Intercellular Adhesion Molecule-1 can promote inflammation(293). Endoglin+ microparticles were also found to be elevated in patients with pulmonary hypertension due to chronic thromboembolic disease compared to healthy control subjects. This might represent a protective/reactive mechanism as in vitro endoglin promoted angiogenesis and increased the life of cultured endothelial cells(294).

7. Prognostic value of microparticles

Several studies have demonstrated an association between microparticles and outcomes in patients with cardiovascular diseases(Table 10). Coronary artery disease is the most studied condition. From an observational study that recruited patients with cardiovascular risk factors and stable coronary artery disease, CD31+/annexin V+ microparticles (apoptotic endothelial & platelet derived microparticles) levels were correlated with higher risk of major adverse cardiovascular and cerebrovascular events and the need for revascularization(295). In patients with ST elevation myocardial infarction post primary angioplasty, high levels of monocyte derived microparticles were strongly related with poor long term survival(296). Additionally, post angioplasty levels of erythrocyte derived microparticles in ST elevation myocardial infarction patients were higher compared to healthy individuals and associated with higher risk of major adverse cardiovascular and cerebrovascular events(297). Increased tissue factor+ microparticle levels were also related with poor outcomes in patients with acute coronary syndrome (unstable angina or acute MI)(298).

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Montoro-Garcia et al(263) reported that in patients with non-ST elevation myocardial infarction, levels of endothelial and monocyte derived microparticles were associated with a higher risk of future admissions due to left ventricular failure and levels of platelet derived microparticles with a higher risk of major haemorrhagic events(263). Higher counts of endothelial derived microparticles were also associated with worse outcomes in patients who presented with cardiac sounding chest pain and underwent coronary angiography for further evaluation(299).

Apart from coronary artery disease, several studies reported association between microparticles and outcomes for patients with heart failure. In acute decompensated heart failure due to coronary artery disease the levels of endothelial derived microparticles (CD31+/Annexin V+) were related with increased mortality within the 3-year follow up period(300). Bulut et al(279) reported similar findings in patients with ischaemic cardiomyopathy. The ratio of endothelial progenitor cells to endothelial derived microparticles (CD31+/Annexin V+) was decreased in the cardiomyopathy group compared with patients with stable 3 vessel coronary artery disease and preserved left ventricular systolic function, suggesting that apart from endothelial dysfunction there is impaired vascular repair capacity. Worse outcomes were also described in patients with left ventricular assisting devices and elevated phosphatidylserine/Annexin V+ microparticles(301). Finally, patients with pre-capillary pulmonary hypertension prior to treatment, high levels of CD62E+ endothelial derived microparticles were associated with higher risk of death and hospitalization due to right heart failure(302).

(Table 10)

8. Conclusion

Microparticles appear to be key players in important biological functions and to have fundamental role in many cardiovascular pathophysiological mechanisms. Abnormal production of microparticles as result of different risk factors leads to inflammation, thrombosis and endothelial damage (Figure 6). The consequences of these pathological processes is the manifestation of cardiovascular disorders. Alternative, microparticles may be generated due to various cardiovascular conditions and their levels reflect disease activity and

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severity. As the knowledge of their functions expands, their role as biomarker is rising. Research data suggest that levels of microparticles also indicate prognosis. An important issue, however, is that there is no standardised analysis technique for microparticles which results in a large diversity of data. This makes difficult to compare results from different analyses and each study should be interpreted separately. Beyond that limitation, microparticles seem to move slowly from research towards clinical level. However, further research is needed in order to guide clinicians how to use microparticles as biomarkers in several cardiovascular diseases and tailor treatments according to individual response and prognosis.

Declaration of interest

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Figure 1. Extracellular vesicles

1: Production of microparticles after stimulation of paternal cell. Microparticles are released from activated cell after outwards rearrangement of the cellular membrane.
2: Production of microparticles during apoptotic process. Microparticles are released before the formation of apoptotic bodies
3: Endosomes in multivesicular body. After exocytosis of the endosomes into the extracellular environment may be called exosomes

Figure 2. Mechanisms involved in the generation of the Microparticles

1: After activation of the cell an increased Ca^{+2} influx follows.
2: Externalisation of phosphatidylserine mediated by ATP-dependent floppases, scramblases and membrane pores
3: Cytoskeleton Protein reconfiguration in order to produce outward membrane blebs.

Capsases, caplains and Rho kinases are involved in the process

Figure 3. Microparticle content

External surface of plasma membrane in general contains negatively charged phosphatidylserine along with membrane proteins like major histocompatibility complex molecules, integrins and tissue factor. In the cytosol, there is no organised nucleus but apart from cytoskeleton proteins and enzymes, nucleic acid remnants (DNA or RNA) are present.

Figure 4. Mechanisms and molecules related with Microparticle induced coagulation

Abbreviations: PS phospatildylserine; GLA γ-carboxyglutamic acid; clotting proteins factors VII, IX, X, and prothrombin.

Negatively charged PS electrostatically attract the positively charged segment of clotting proteins/GLA complex and induce thrombogenesis. Tissue factor may also activate the coagulation cascade via the FVII/VIIa complex. Additionally, inhibition of fibrinolysis by microparticle membrane proteins such as plasminogen activator inhibitor-1 and protein S may augment thrombogenesis.

Figure 5. Mechanisms associated with initiation and progression of atherosclerosis mediated by Microparticles (MPs)

Figure 6. Cardiovascular diseases and microparticles

Flow chart which summarises the role of microparticles in the genesis (related with several risk factors) and manifestation of cardiovascular diseases. Utilisation as biomarkers to assess disease activity/severity, prognosis and treatment guidance is emerging as detection and enumeration methods for microparticles are improving.

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Table 1. Stimuli causing generation of microparticles in vitro or in vivo(37)(20)						
Type of cell	**Endothelial cell**	**Platelet**	**Neutrophil**	**T-Cell**	**Monocyte and Macrophage**	**Smooth cell**
Stimuli						
	Modified LDL	Flow conditions	Pro-inflammatory cytokines	Pro-inflammatory cytokines	Cigarette extract	Modified LDL
	HDL cholesterol	Thrombin		Phytohemagglutinin	Pro-inflammatory cytokines	HDL cholesterol
	Uremic toxin	Collagen	Phorbol myristate acetate	Staurosporin	Calcimycin	
	Flow conditions	Homocysteine		Etoposide		Flow conditions
	Thrombin	Pro-inflammatory cytokines	Anti-neutrophil cytoplasmic antibodies	Actinomycin D	Lipopolysaccharides	Activated protein C
	Homocysteine	Calcimycin	Bacterial infection	Phorbol myristate acetate	Etoposide	Pro-inflammatory cytokines
	Activated protein C	collagen	N-Formyl-Methionyl-Leucyl-Phenylalanine		Fas Ligand	Fas-ligand
	Plasminogen activator inhibitor	Lipopolysaccharides				Platelet derived growth factor
	Pro-inflammatory cytokines[a]	Shiga toxin				
	Oxidative stress	sCD40 Ligand				
	High glucose	Erythropoietin				
	Uremic toxins	Noradrenaline				
	Lipopolysaccharides	acid phosphatase 5				
	Camptothecin	Reactive oxygen species				
	Angiotensin II					
	Plasminogen Activator Inhibitor 1					
	C Reactive Protein					

[a]: tumor necrosis factor a, Interleukin 1b, Interleukin 6,

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Table 2. Main antigen markers used for MP cell origin determination	
Cell	Cluster of differentiation (CD)
Endothelial	CD31(59)
	CD51(60)
	CD105(61)
	CD62E(61)
	CD144(62)
	CD34(63)
Platelet	CD41(64)
	CD42a(65)
	CD42b(66)
	CD61(63)
Red Cell	CD235(67)
Leukocyte	CD45(67)
Monocyte	CD14(68)
Neutrophil	CD66b(64)
T cell	CD4(69)
	CD8(70)
CD31, CD51, CD105 are not specific for endothelial cells. CD31 is also expressed on platelets, CD51 on platelets and macrophages and CD105 in activated monocytes/macrophages. For MP detection, markers are usually combined to discriminate this population from other MPs. For example, platelet MPs are CD31 positive / CD42b positive whereas endothelial MPs are CD31 positive / CD42b negative.	

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Table 3. Bioactive molecules of microparticles		
Molecule	**Type of cell producing Microparticles**	**Target cell or environment**
Receptor/Membrane molecule		
chemokine receptor CCR5(74)	peripheral blood mononuclear cells	Various cells
CXCR4 receptor(82)(83)	Platelets	Various cells
Glycoprotein IIb/IIIa receptors(84)	Platelets	neutrophils
oncogenic receptor EGFRvIII (epidermal growth factor receptor variant III) (85)	Tumor Cells	Various cells
major histocompatibility complex (MHC) class II(73)	Immune cells	Immune cells
Tissue Factor(48)	Monocytes	Platelets
Peroxisome proliferator-activated receptor gamma(86)	Platelets	Monocytes
Cytokines		
interleukin-1beta(87)(76)(75)(88)	Various cells	Various cells
Chemokine (C-C motif) ligand 5(89)	Platelets	Endothelial cells
Growth factors		
Vascular endothelial growth factor(90)(91)(92)	Platelets/Tumor Cells	Endothelial cells
Basic fibroblast growth factor(90)(91)	Platelets/Tumor Cells	Endothelial cells
Platelet-derived growth factor(91)	Platelets	Endothelial cells
Lysis enzymes		
Matrix metalloproteinases(92)	Tumor Cells	extracellular matrix
Extracellular matrix metalloproteinase inducer(93)	Tumor Cells	extracellular matrix
Caspase 1(94)	Monocyte	Smooth muscle cell
Lipids		
Arachidonic acid(79)(80)(95)	Platelets	Various cells
Platelet activated factor(96)(97)	Various cells	Platelets
Ribonucleic acid (RNA)		
Messenger RNA(98)(38)	Stem cells	Various cells
Micro RNA(99)(100)(101)	Stem cells	Various cells

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Table 4. Inflammation and Microparticles (MPs)		
Type of cell producing MPs	Target cell	Molecules involved in the pathogenesis of inflammation mediated by MPs
		Cytokines
Endothelial	Various inflammatory cells	IL-1β and TNF-α(114)
Leucocytes	Endothelial	IL-6 and MCP-1(115)
T cells	monocytes	IL-8, TNF-a and IL-1β(43)(116)
		Adhesion molecules
Monocytes Platelet	endothelial	intercellular adhesion molecule-1, vascular cell adhesion molecule-1 E-selectin(117)(95)
		lipids
Platelet	endothelial	thromboxane A2 and cyclooxygenase(79)
		Other
Polymorphonuclear	macrophage	transforming growth factor beta1(118)
		Annexin V(119)
Monocytes	macrophage	peroxisome proliferator-activated receptor gamma protein(120)
Polymorphonuclear	Various cells	complement proteins (C1q)(51)
Abbreviations: IL interleukin, TNF tumor necrosis factor, MCP-1 Monocyte chemoattractant protein-1,		

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Table 5. Angiogenesis and Microparticles (MPs)		
Type of cell producing MPs	Target cell or environment	Molecules involved in the angiogenesis mediated by MPs
Promotion of neovascularisation		
Platelets	Human umbilical vein endothelial cells	bioactive lipids(90)(121)
Platelets	Ischaemic myocardium	vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), inhibition of platelet factor-4(91)
Various cells expressing membrane Tissue Factor	Endothelial	beta1-integrin, extracellular signal regulated kinase(122)
T-cells	Endothelial	Activation of morphogen Sonic Hedgehog (Shh) pathway which promotes synthesis of adhesion molecules and proangiogenic factors(123)(124)
Endothelial	Endothelial	Plasmin activating factors(125)
Endothelial	Matrix	metalloproteinases(126)
Endothelial	endothelial	Messenger RNA(127)
Adipose cells	Human umbilical vein endothelial cells	Leptin, fibroblast growth factor alpha (FGFa), Tumor Necrosis Factor a, matrix metalloprotease (MMP)-2 and MMP-9 mediated activation(128)
Inhibition of neovascularisation		
Lymphocyte	Endothelial	CD36 antiangiogenic receptor(132)
Abbreviations: CD cluster of differentiation, RNA Ribonucleic acid		

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Table 6. Studies with Microparticles (MPs) in Diabetic populations or high glucose concentration conditions		
Type of MPs	Conclusion	Reference
Endothelial derived microparticles CD62E positive, CD62P positive, CD142 positive, CD45 positive circulating MPs, their apoptotic (AnnexinV positive) fractions and miRNA-126 expression.	CD62E positive MPs level and miR-126-3p content in MPs are abnormal in subjects with pre-diabetes.	Giannella A et al(163)
CD3 positive T- Lymphocyte MPs, CD105 positive EMPs, Annexin V positive MPs, CD31 positive MPs, CD41a positive and Annexin V/CD31/ CD41a positive	Increased number of MPs in diabetic patients compare with healthy control group	Kurtzman N et al. (164)
PMPs	Association with vascular changes in T2DM/ endothelial dysfunction and activated platelets/PMPs	Nomura S et al.(166)
Monocytes derived MPs Annexin V/CD14 positive, PMPs GPI positive	higher in diabetic patients of with related vascular complications	Omoto S et al(167)
annexinV positive, PMP CD31/CD42 positive, LMP CD45positive , CD31positive/CD42negative EMP, CD51positive EMP	MPs increased in patients with T2DM. EMPs levels are associated with vascular dysfunction.	Feng B et al(61)
CD36 positive	CD 36 positive MPs in DM patients were from erythrocyte origin compare with healthy subjects, originated from endothelial cells.	Alkhatatbeh MJ et al(168)
PMPs CD41 positive, EMPs CD51 positive, leukocytes derived MPs CD45 positive, neutrophil derived MPs CD66b positive, monocyte derived MPs CD14 positive and total annexin V-positive MPs.	Different phenotypes identified between T1, T2 DM and healthy subjects. Differences in properties and particularly the procoagulant activities.	Sabatier F et al(65)
Annexin V positive, MPs from non- activated platelet (CD41positive), MPs from activated platelets (CD62p positive), EMPs (CD144 positive)	MPs properties and type (composition, content and cellular origin) are related with the type of vascular complications due to DM.	Tsimerman G et al(173)
MPs from Human umbilical vein endothelial cells	Raised glucose levels is a potent stimulus for MP formation that affects their molecular composition and may cause endothelial injury	Burger et al. (172)

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PMPs CD41 positive, Annexin V MPs, MPs expressing tissue factor (CD142)	DM is associated with high levels circulating MPs with procoagulant features	Tripodi A et al(174)
EMPs CD144 positive, PMPs CD42b positive, monocyte derived MPs CD14 positive	MPs from T1DM patients promoted platelet/endothelial cell interaction with an intensity correlated with the degree of the associated vascular complications	Terrisse Ad et al(67)
Lymphocyte and plasma MPs (Surface markers: CD3, CD11a, GP1b, CD31)	Lymphocyte-derived MPs from diabetic patients or in vivo circulating MPs from diabetic patients reduced endothelial NO synthase expression.	Martin S(138)
Surface markers: CD41a, CD64, CD144, CD144/CD31, Annexin V, CD144/annexin V and CD144/CD31/annexin V.	Apoptotic endothelial cell-derived were significantly increased in diabetic patients and associated with asymptomatic atherosclerosis	Berezin et al. (178)
human coronary endothelial cells derived MPs	High glucose environment increases NADPH oxidase activity in EMPs and promotes endothelial dysfunction	Jansen F et al(177)
EMPs (surface markers: CD31, CD42b, annexin V, and CD62E)	EMP levels are associated with different risk of diabetic vascular complications	Jung K-H et al(60)
PMPs CD41 (GPIIb) positive, EMPs CD144 (VE-Cadherin) positive	Unstable coronary artery plaques in diabetics are associated with elevated EMPs	Bernard S et al(63)
PMPs (Surface marker: antiplatelet GPIX monoclonal antibody)	Plasma PMPs are significantly higher in patient with DM compare with normal controls. Antiplatelet therapy reduces the level of PMPs.	Omoto S et al(169)
EMPs CD 144 positive, Monocyte derived MPs CD 14 positive, PMPs tissue factor and CD 41 positive	Normalisation of glycaemic control in DM patients after bariatric surgery leads to reduction of the MPs levels	Cheng V et al(69)
PMPs, T-lymphocytes derived MPs and leukocyte derived MPs	TF on MPs from DM patients may be involved in	Diamant M et al(70)

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(surface markers: quadruple-stained with annexin V, CD61, anti-TF, and CD15 (ligand for P-selectin), CD66e (granulocytic marker), or CD62P (P-selectin), or with CD4 (T-lymphocytes), anti-TF, and CD11b (leukocyte marker)	processes other than coagulation such as angiogenesis	
TF bearing MPs from human renal mesangial cells and human dermal microvascular endothelial cells	MPs expressing TF might be a mediator to neovascularisation due to elevated glucose levels	Ettelaie C et al(179)
MPs from Human umbilical vein endothelial cells	Reduction of miR-126 from plasma vesicles might explain the impaired neo-angiogenesis in DM patients	Zampetaki A et al(181)
CD cluster of differentiation, EMP endothelial derived MP, PMP platelet derived MP, T2DM Type 2 diabetes mellitus, , GP glycoprotein, LMP leukocyte derived MP, TF Tissue factor, miR micro Ribonucleic acid, NADPH Nicotinamide adenine dinucleotide phosphate, NO Nitric monoxide		

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Table 7. List of medications induced reduction of Micproparticle (MP) levels in diabetic populations			
Medication category	Pharmacological name	Type of MPs investigated	Other co-morbidities apart from DM
Antiplatelet	Cilostazol(184)	PMPs GPIX positive	
	Ticlopidine(185)(186)(187)	PMPs GPIX positive , Monocyte derived MPs CD14 positive	Hyperlipidemia
	Sarpogrelate(188)	PMPs	
	Aspirin & Clopidogrel(189)	PMPs CD151 positive, Monocyte derived MPs CD14 positive	TIA
Antihypertensive	Efonidipine(190)	PMPs GPIX positive, Monocyte derived MPs CD14 positive	HTN
	Nifedipine(191),(192)	PMPs GPIX positive, Monocyte derived MPs CD14/ Annexin V positive, EMPs CD51/ Annexin V positive	HTN
	Losartan(193)(194)	PMPs GPIX positive, Monocyte derived MPs CD14/ Annexin V positive, EMPs CD51/ Annexin V positive	HTN
	Valsartan(195)	Monocyte derived MPs CD14/ Annexin V positive	HTN
Anti-lipidaemic	Pitavastatin(196)	PMPs CD42b and CD42a (glycoprotein Ib and IX) positive	Hyperlipidemia
	Pravastatin(71)	MPs derived from: platelets (CD61 positive),	Hyperlipidemia

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		T-helper cells (CD4 positive), T-suppressor cells (CD8 positive), monocytes (CD14 positive), B cells (CD20 positive), endothelial cells (CD62e positive), erythrocytes (glyco-A positive) and granulocytes (CD66b positive), annexin V and TF positive MPs	
	Simvastatin (193)(194)	PMPs GPIX positive, Monocyte derived MPs CD14/ Annexin V positive, EMPs CD51/ Annexin V positive	Hyperlipidemia, HTN
	Atorvastatin(197)	PMPs, surface markers CD42a (Glycoprotein IX), together with either CD61 (GPIIIa), CD62P (P-selectin) or CD142 (TF)	Hyperlipidemia
	Bezafibrate(198)	PMPs CD42b positive	Hyperlipidemia
	Probucol(185)	PMPs GPIX positive , Monocyte derived MPs CD14 positive	Hyperlipidemia
	Eicosapentaenoic acid(196)(199)(200)	PMPs CD42b and CD42a (glycoprotein Ib and IX) positive	Hyperlipidemia
	Vitamin C(201)	EMPs CD31 positive, PMPs GPIb positive	Acute myocardial infarction

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Antidiabetic	Acarbose(202)	PMPs CD42b and CD42a (glycoprotein Ib and IX) positive	
	Miglitol(203)	PMPs CD42b and CD42a (glycoprotein Ib and IX) positive	
	Pioglitazone(204)	EMPs CD31 positive	
Abbreviations: CD cluster of differentiation, HTN Hypertension, EMP endothelial derived MP, PMP platelet derived MP , GP glycoprotein, TF Tissue factor, DM diabetes mellitus			

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Table 8. Studies with Microparticles (MPs) in Acute Coronary Syndrome populations (ACS)		
Type of MPs	Conclusion	Reference
Surface markers: Anexin V, anti-CD3, anti-CD11a, anti-CD31, anti-CD146, and anti-GP Ib	Higher levels of procoagulant EMPs in Patients with ACS compare with patients with no CAD or SA	Mallat Z et al(259)
Combination of CD31 (PECAM-1) or CD51 (aV□3, vitronectin receptor) with CD42. EMPs and PMPs (PMPs CD42 positive)	EMPs were elevated in patients with CAD compared with control subjects, CD31□EMPs higher in patients with ACS compare with SA, among patients with a first MI, CD31 EMPs released in ACS and CD51 released in SA.	Bernal-Mizrachi L et al(260)
Leukocyte derived MP CD11a positive , EMPs CD31 positive, PMPs GPIb positive, Anexin V positive	Early decrease of procoagulant MPs in patients with STEMI treated with PPCI and abciximab compare with patients treated only with PPCI.	Morel O et al(261)
EMPs CD146 and CD 106 (VCAM-1) positive	High density of VCAM-1 expressed on EMPs from patients with ACS	Radecke CE et al(262)
Annexin V-binding MPs, MPs CD42b positive, EMPs CD144 positive and monocyte derived MPs CD14 positive	In NSTEMI, EMP and monocyte derived MPs were independently predictive for future admissions related to heart failure and PMPs for major bleedings	Montoro-García S et al(263)
EMPs CD144 positive, PMPs CD41 positive and leukocyte-derived MPs CD45 positive	Variation of levels of different origin MPs associated with time in patients before and	Zhou B et al(264)

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	after PPCI	
Surface markers : anti-CD11a (leukocytes), anti-CD31 (endothelial cells), anti-CD42b (endothelial cells), and anti-CD146 (platelets), Anexin V for apoptotic MPs	Increased levels of MPs in culprit coronary arteries after STEMI and significant reduction after successful PCI	Min P-K et al(266)
Lymphocyte derived MPs CD45/CD3 positive, monocyte derived MPs CD14 positive, EMPs CD146 positive or CD62e positive, granulocytes derived MPs CD66b positive, other surface markers: CD142 (TF), Anexin V, CD31	Increased levels of MPs in culprit coronary arteries after STEMI, levels of MPs positively correlated to time of revascularisation post STEMI	Suades R et al(267)
EMPs CD31 positive/CD42 negative, PMPs CD31 positive/CD42 positive, anexin V positive	ACS are associated with higher levels of circulating MPs compare with SA patients. In SA the degree of atherosclerotic plaque is not related with the levels of plasma MPs	Biasucci LM et al(268)
TF positive MPs	Thrombolysis failure in acute MI is associated with higher levels of procoagulant MPs	Huisse M-G et al(265)
TF positive MPs	MPs were lower as the severity of the stable angina/ACS was increasing (stable CAD vs UA vs MI)	Maly M et al(270)
PMPs CD42 positive, Leukocyte derived MPs	Increased levels of MPs in ACS and positive correlation	Stępień E et al.(64)

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CD45 positive , Monocyte derived MPs CD14 positive, EMPs CD31, CD51/61, CD34 positive and activated tissue factor positive (TF) MPs	of MP levels with platelet activation markers	
EMPs CD31 positive/ CD42negative and CD144 positive, PMPs CD31/CD42 positive	EMPs and PMPs reflect the size of myocardium at risk in patients with STEMI	Jung C et al(269)
Abbreviations: CD Cluster of differentiation, EMP endothelial MP, STEMI ST elevation myocardial infarction, PPCI primary percutaneous coronary intervention , TF tissue factor, PMP platelet derived MP, CAD coronary artery disease, NSTEMI non- ST elevation myocardial infarction, SA stable angina, VCAM-1 Vascular cell adhesion protein 1, PECAM-1 Platelet endothelial cell adhesion molecule-1		

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Table 9. Studies with Microparticles (MPs) in Heart Failure		
Type of MPs	Conclusion	Reference
Annexin V-binding MPs, MPs CD42b positive, EMPs CD144 positive and monocyte derived MPs CD14 positive	In NSTEMI, EMP and monocyte derived MPs were independently predictive for future admissions related to heart failure	Montoro-García S et al(263)
Annexin V-binding MPs, MPs CD42b positive, EMPs CD144 positive	Annexin V-MPs levels appear to reflect accurately the acute decompensated phase in systolic heart failure	Montoro-García S et al(281)
CD 31/Annexin V positive	EMPs was increased in patients with LV dysfunction compared with those with normal or preserved LV function.	Bulut D et al(279)
Surface markers for EMPs: CD31 (platelet endothelial cell adhesion molecule [PECAM]-1), CD144 (vascular endothelial [VE]-cadherin), CD62E (E-selectin) and annexin V	EMPs levels are higher in patients with HFrEF and increased Body Mass Index (BMI>25kg/m2) compare with other patients with lower BMI.	Berezin AE et al(280)
Surface markers for EMPs: CD31, CD62E, CD105, Annexin V	Adding CD31/annexin V positive EMPs to CD14/ CD309 positive cell ratio to other variables predict the risk of HFpEF.	Berezin AE et al(62)
EMPs CD31/CD62E positive	EMPs in post-transplant patients are consistent with increased apoptotic activity	Garcia S et al(282)
Red blood cell derived MPs (CD235 positive), leukocyte MPs (CD45 positive), platelet (CD31/CD41positive) and EMPs (CD31 positive/CD41 negative, CD62e positive, CD144 positive)	All types of MPs were elevated in patients with LVAD compare with patients with CAD and healthy subjects due to haemolysis and disturbed endothelial integrity	Sansone R et al(68)
EMPs	LVAD do not cause vascular damage 3 months after implantation.	Ivak P et al(283)
Surface markers for EMPs: CD31, CD41a, CD64, CD105, CD144, CD62E and Annexin V. PMPs CD41a positive	Patients with HF and metabolic syndrome have higher levels of CD31/Annexin V positive EMPs in addition with lower levels of CD62E positive EMPs compare with healthy subjects.	Berezin AE et al(66)
Surface markers: CD31, CD144, CD62E, CD14, CD45, Annexin	Patients with PPCM appears to have elevated levels of	Walenta K et al(284)

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V, CD62P, CD42b	activated EMPs (CD144 positive) and PMPs (CD42b positive) compare with patients with ischaemic cardiomyopathy	
Abbreviations: CD cluster of differentiation, EMP Endothelial derived MP, NSTEMI non ST elevation myocardial infarction, PMP platelet derived MP, HFrEF heart failure with reduced enjection fraction, HFpEF heart failure with preserved enjection fraction, LV left ventricle, LVAD LV assisting device, CAD coronary artery disease, BMI body mass index, PPCM post partum cardiomyopathy.		

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Table 10. Studies where Microparticle levels are associated with outcomes		
Type of MPs	Prognostic value	Reference
Annexin V-binding MPs, MPs CD42b positive, EMPs CD144 positive and monocyte derived MPs CD14 positive	In NSTEMI, EMP and monocyte derived MPs were independently predictive for future admissions related to heart failure	Montoro-García S et al(263)
EMPs apoptotic CD31/Annexin V positive	CD31/Annexin V positive MPs is an independent predictor of MACCE in stable CAD patients	Sinning J-M et al(295)
Monocyte-derived MPs (Surface markers: CD14+, CD14/CD11b and CD14/CD142)	Monocyte-derived MPs levels assessed in the acute phase of STEMI are related to the prognosis of long term CV death	Chiva-Blanch G et al(296)
Annexin V positive, CD41 positive PMPs, CD235a positive erythrocyte derive MPs	CD235a positive erythrocyte derive MPs concentrations appear to be positively associated with MACCE in patients with STEMI and PPCI	Giannopoulos G et al(297)
Surface markers: Annexin V, TF , CD41, CD66b	In the plasma of patients with ACS, the TF activity is a consequence of circulating MPs and is an independent predictor for MACCE	Steppich BA et al(298)
EMPs CD146, CD31	Higher EMP levels had a higher risk of MACCE in ACS patients.	Fan Y et al(299)
EMPs CD31/Annexin V positive	EMPs levels were associated with increased mortality and recurrent hospitalization due to CHF	Berezin AE et al(300)
Apoptotic MPs Annexin V positive	elevation of apoptotic MP levels in LVAD-supported patients are associated with increased risk for adverse events.	Nascimbene A et al(301)
EMPs CD62e positive, CD144 positive, CD31 positive (+)/CD41 negative leukocytes-derived MPs CD45 positive	Elevated levels of CD62e positive EMPs in PHTN patients prior to treatment are associated with adverse clinical events	Amabile N et al(302)
Abbreviations: MACCE Major adverse cardiovascular and cerebral event , CD cluster of differentiation, EMP endothelial derived MP, NSTEMI non-ST elevation myocardial infarction, CAD coronary artery disease, STEMI ST elevation myocardial infarction, CV cardiovascular, TF tissue factor, ACS acute coronary syndrome, LVAD Left ventricular assisting device, PHTN pulmonary hypertension		

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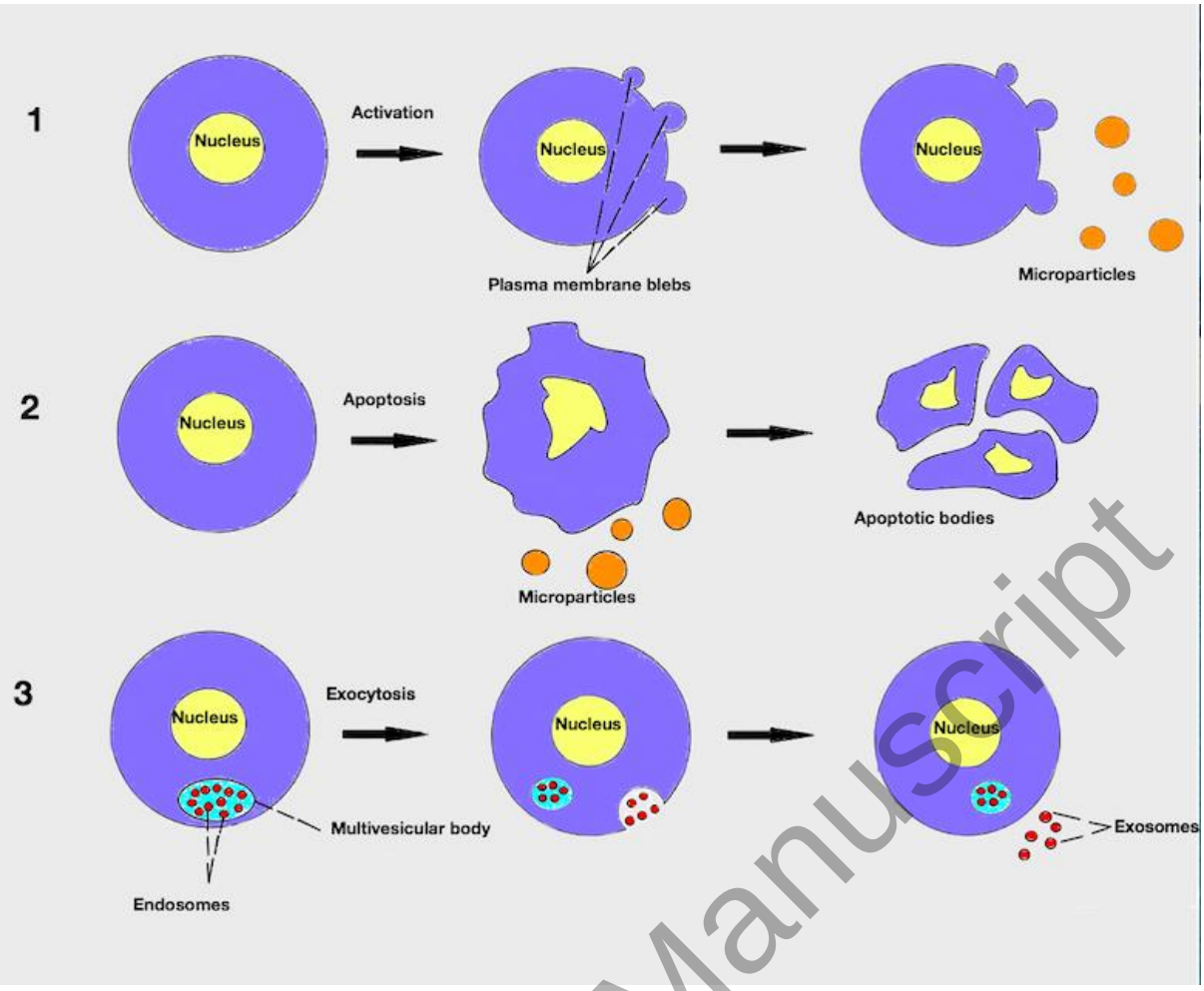

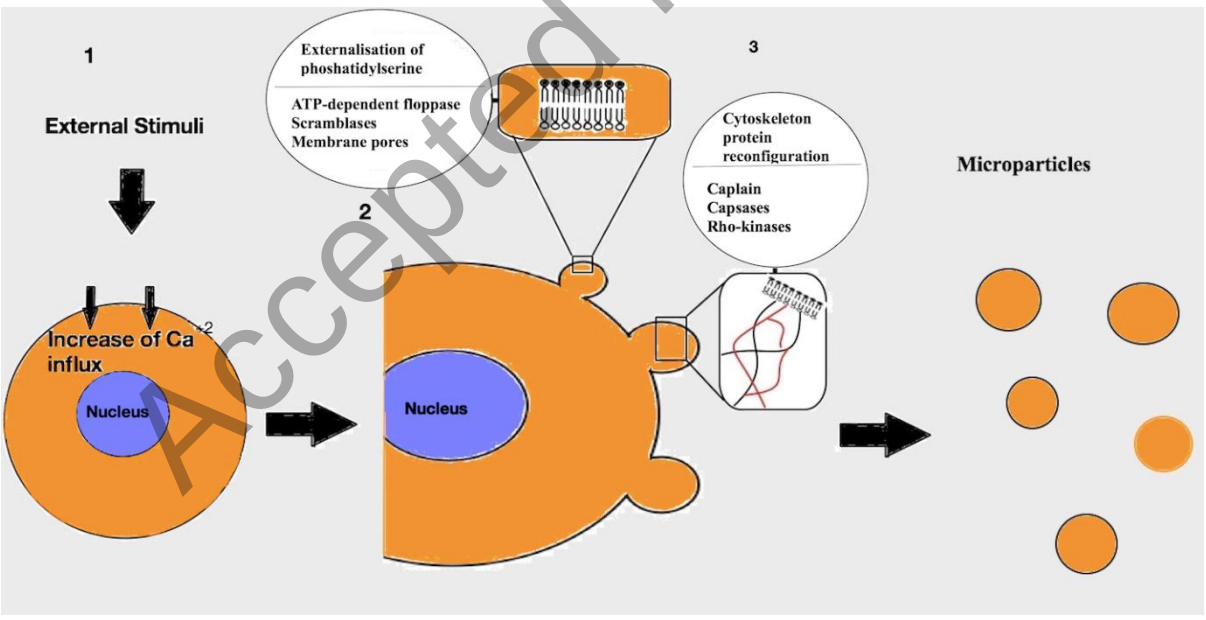

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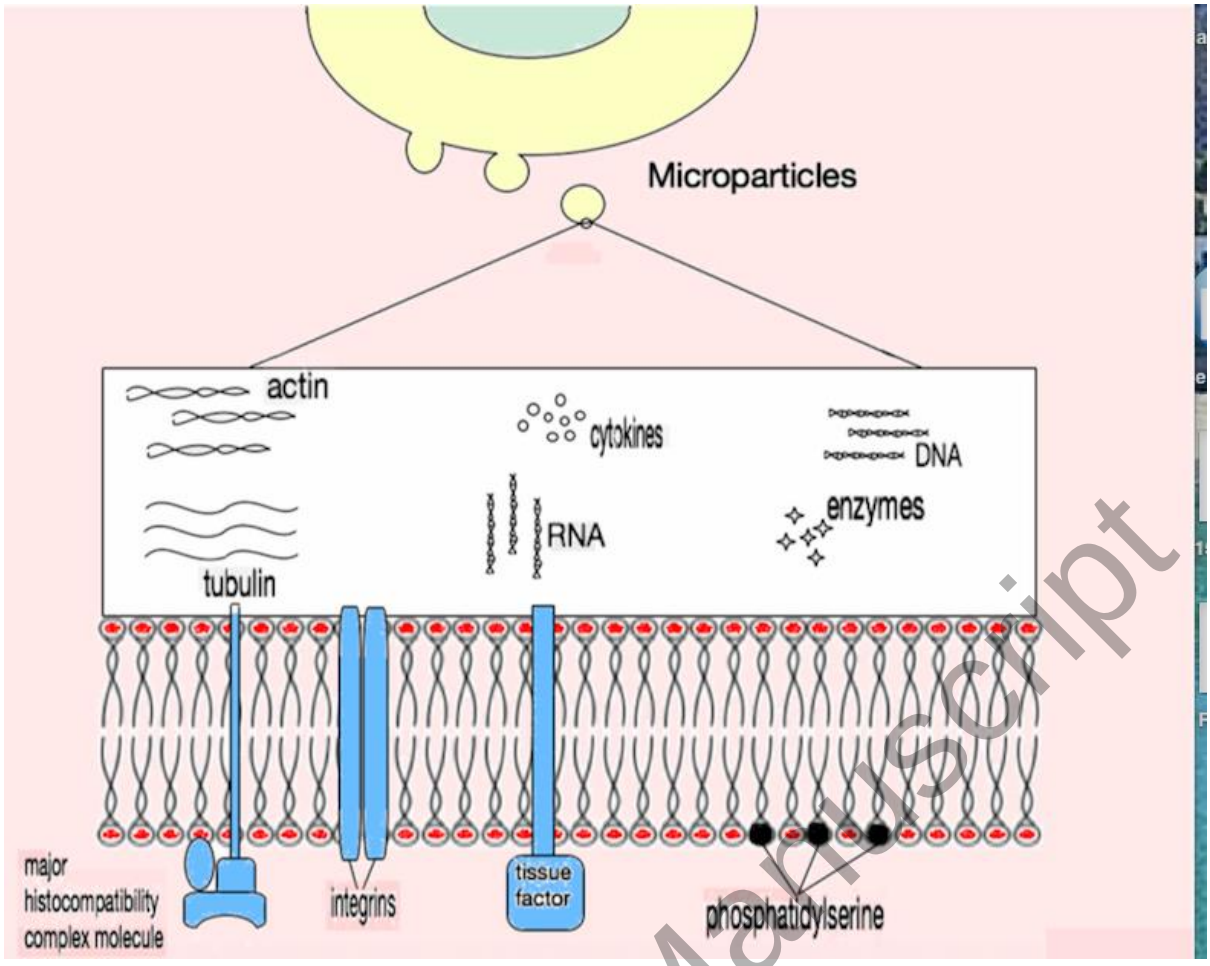

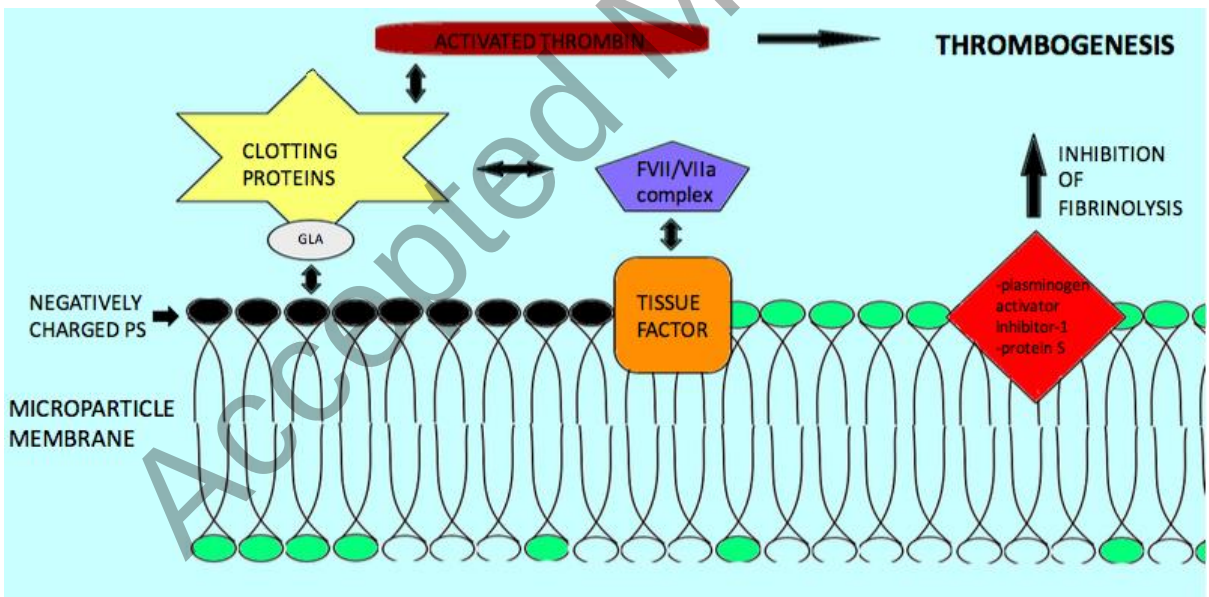

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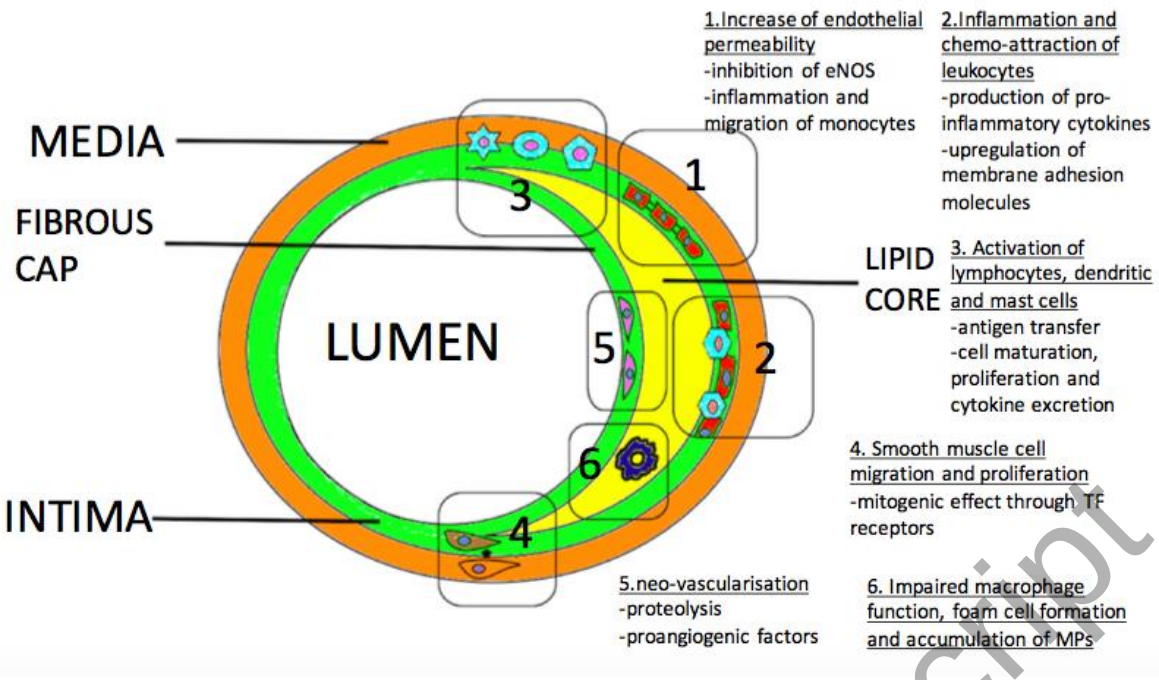

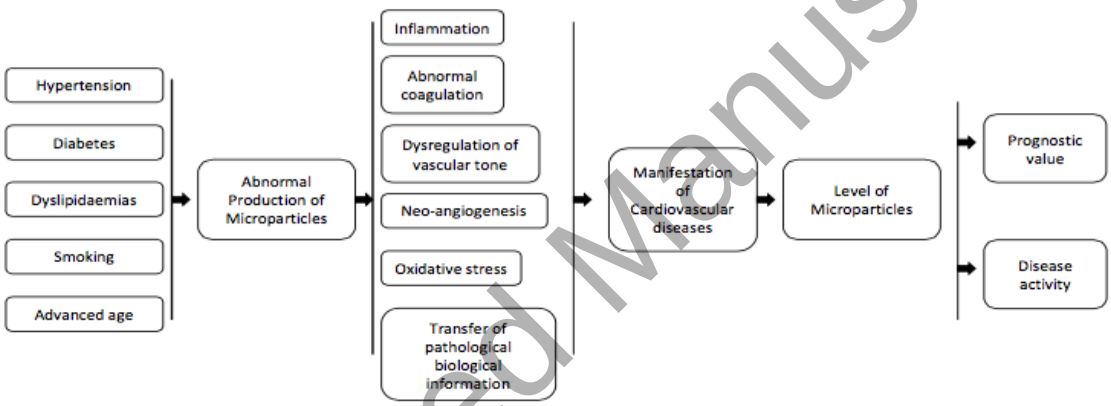

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