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Review

Cardiovascular risk assessment in patients with rheumatoid arthritis: The relevance of clinical, genetic and serological markers

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ABSTRACT

Cardiovascular disease (CV) is the most common cause of premature mortality in patients with rheumatoid arthritis (RA). This is the result of an accelerated atherosclerotic process. Adequate CV risk stratification has special relevance in RA to identify patients at risk of CV disease. However, current CV risk screening and management strategies underestimate the actual CV risk in RA. Consequently, the search for additional tools that may help to identify those patients at high CV risk has become a key objective in the last years. In this regard, non-invasive surrogates, such as carotid ultrasonography, have been found to be excellent predictors of future CV events. In addition, several studies have revealed the relevance of a genetic component in the development of CV disease in RA patients. Besides an association with *HLA-DRB1** shared epitope alleles other gene polymorphisms located inside and outside the HLA seem to influence the risk of cardiovascular disease in RA. Moreover,

Abbreviations: ABO, histo-blood group ABO system transferase; ACP1, acid phosphatase locus 1; ADAMTS7, metallopeptidase with thrombospondin type 1 motif 7; ADIPOQ, adiponectin; ADMA, asymmetric dimethylarginine; Angpt-2, angiopoietin-2; ANKS1A, ankyrin repeat and sterile alpha motif domain containing 1A; anti-CCP, anti-cyclic citrullinated peptide; ASCL1, achaete–scute complex homolog 1; ATM, atherothrombotic manifestations; CARD8, caspase recruitment domain-containing protein 8; CCR5, C-C chemokine receptor type 5; CD40L, CD40 ligand; cIMT, carotid intima–media thickness; CRP, C-reactive protein; CSFs, colony-stimulating factor; CV, cardiovascular disease; CVA, cerebrovascular accident; CIITA, class II transcriptional activator; CXCL12, C-X-C motif chemokine ligand 12; CYP17A1-CNNM2-NT5C2, cytochrome P450 family 17 subfamily A member 1-cyclin and CBS domain divalent metal cation transport mediator 2-5′-nucleotidase, cytosolic II; DNA, deoxyribonucleic-acid; EDNRA, endothelin receptor type A; eNOS, endothelial nitric oxide synthase; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FMD, flow mediated endothelium-dependent vasodilatation; GCKR, glucokinase regulator; GH, growth hormone; GHSR, growth hormone secretagogue receptor; GWAS, genome-wide association studies; HDL, high-density lipoproteins; HHIPL1, hedgehog interacting protein-like 1; HLA, human leukocyte antigen; HNF1A, hepatic nuclear factor 1-α; HNF4A, hepatocyte nuclear factor 4-α; HOMA, homeostatic model assessment; ICAM, Intercellular adhesion molecule; IFN-ϒ, Interferon gamma; IHD, ischaemic heart disease; IL, interleukin; IL1F10, interleukin-1 family member 10; IL-1RAcP, IL-1 receptor accessory protein; IL-1RL1, IL-1 receptor like 1; IL-6R, IL-6 receptor subunit; IL-6ST, interleukin 6 signal transducer; iNOS, inducible nitric oxide synthase; IR, insulin resistance; IRF5, interferon regulatory factor 5; JAK, Janus kinase; LDL, low-density lipoprotein; LEP, leptin; LEPR, leptin receptor; LPA, lipoprotein(a); LTA, lymphotoxin α; MAP, mitogen activated protein; MetS, metabolic syndrome; MHC2TA, class II, major histocompatibility complex transactivator; MI, myocardial infarction; MIA3, melanoma inhibitory activity family member 3; MIF, macrophage migration inhibitory factor; MRAS, muscle RAS oncogene homolog; MRPS6, mitochondrial ribosomal protein S6; MSRA, methionine sulfoxide reductase A; MTHFR, methylene tetrahydrofolate reductase; NAMPT, nicotinamide phosphoribosyl transferase; NF-κB, nuclear factor-κB; NLRP3, NLR family, pyrin domain containing 3; nNOS, nitric oxide synthase neuronal; NO, nitric oxide; NOS, nitric oxide synthase; OPG, osteoprotegerin; PCSK9, proprotein convertase subtilisin/kexin type 9; PIK3CG, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma; PON1, paraoxonase 1; PPAP2B, phosphatidic acid phosphatase type 2B; PPP1R3B, protein phosphatase 1, regulatory-inhibitor- subunit 3B; PSRC1-CELSR2-SORT1, proline/serine-rich coiled-coil 1-cadherin EGF LAG seven-pass G-type receptor 2-sortilin 1; PTPN22, protein tyrosine phosphatase, non-receptor; RA, rheumatoid arthritis; RASD1-SMCR3-PEMT, RAS, dexamethasone-induced 1-Smith-Magenis syndrome chromosome region candidate 3-phosphatidylethanolamine N-methyltransferase; RETN, resistin; RF, rheumatoid factor; SALL1, sal-like 1; SE, shared epitope; SCORE, systematic coronary risk evaluation; SDMA, symmetric dimethylarginine; SMG6-SRR, SMG6 nonsense mediated mRNA decay factor-serine racemase; STAT, signal transducers and activators of transcription; TCF21, transcription factor 21; TGFB1, transforming growth factor beta 1; TLRs, Toll-like receptors; TNF, tumor necrosis factor; TNFA, tumor necrosis factor alpha; TRAF1/C5, TNF receptor associated factor 1/complement component 5; TRAIL, TNF-related apoptosis-inducing ligand; UBE2Z-GIP-ATP5G1-SNF8, ubiquitin conjugating enzyme E2 Z-gastric inhibitory polypeptide-ATP synthase, H+ transporting, mitochondrial Fo complex subunit C1 (subunit 9)-SNF8, ESCRT-II complex subunit; US, carotid ultrasonography; UTR, untranslated region; VCAM, vascular endothelial adhesion molecule; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor; WDR12, WD repeat domain 12; ZC3HC1, zinc finger C3HC-type containing 1; ZNF259-APOA5-A4-C3-A1, zinc finger protein 259-apolipoprotein A-V-IV-C-III-A-I.

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Rheumatoid arthritis
Serum biomarkers

serum levels of some metabolic syndrome-related biomarkers, adipokines such as adiponectin and biomarkers of endothelial cell activation and inflammation such as Osteoprotegerin and Asymmetric dimethylarginine have recently been found useful for the prediction of CV disease in these patients. An update of the current knowledge on these potential markers, especially focused on new genetic and serological biomarkers is shown in this review.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by chronic and erosive arthritis that mainly involves peripheral joints [1,2]. RA affects activities of daily living, significantly decreasing the quality of life of affected patients. Comorbidity is a major issue in this disorder [1]. Cardiovascular (CV) disease has been described as the main cause of premature mortality [2–6] and sudden death in patients with RA [7]. This is the result of a process of accelerated atherosclerosis [8,9].

Traditional CV risk factors such as smoking, diabetes mellitus, hypertension, dyslipidemia and obesity are independently associated with the development of CV disease [10–13], subclinical atherosclerosis [12–14], and increased risk of CV mortality in patients with RA [15]. Chronic inflammation also appears to play an important role in the development of subclinical atherosclerosis and CV events in patients with RA [12,16–19].

Adequate CV risk stratification has special relevance in RA to identify patients at risk of CV disease. However, current CV risk screening and management strategies underestimate the actual CV risk in RA [20]. Consequently, the search of markers that may help to identify RA patients at high CV risk has become a priority in the last years [21].

Non-invasive, reproducible and cheap clinical surrogates, such as carotid ultrasonography, have been found to be excellent predictors of future CV events [22,23]. Several studies have also revealed the implication of a genetic component in the development of CV disease in RA patients [19,24,25]. Moreover, serum levels of some metabolic syndrome-related biomarkers, adipokines and biomarkers of endothelial cell activation and inflammation have recently been found useful for the prediction of CV disease in these patients [26,27].

An update of the current knowledge on these potential markers, especially focused on new genetic and serological biomarkers is shown in this review.

2. CV burden in RA and clinical surrogate markers of CV disease in RA

Patients with RA are at greater risk of developing CV events [4,6,28]. Patients with RA are at a 50% increased risk of CV mortality compared with the general population [3]. Women with RA were found to have more than 2-fold higher risk of developing myocardial infarction compared with women without this pathology, even after adjusting for potential CV risk factors [29].

Endothelial dysfunction is a systemic pathological state of the endothelium described as an early step in the development of atherosclerosis in RA [17]. In this sense, several mechanisms link systemic inflammation to endothelial dysfunction in these patients [8,30]. Components of the metabolic syndrome that are frequently observed in RA [31,32] such as insulin resistance (IR) and dyslipidemia along with an increased oxidative stress can promote *per se* this process [8,30]. On the other hand, the oxidation of low-density lipoprotein (LDL) induces the production of inflammatory molecules by the endothelial cells [30]. Furthermore, circulating cytokines, especially tumor necrosis factor (TNF)-α, stimulate the diapedesis of monocytes across the endothelium and also reduce the synthesis of nitric oxide (NO) by endothelial cells [8,30].

Endothelial dysfunction may be determined by an impaired ability of the artery to dilate in response to physical and chemical stimuli, due to a decreased release or increased breakdown of NO [33]. Additionally, this process can be non-invasively determined by flow mediated endothelium-dependent (FMD) vasodilatation using high-sensitivity brachial ultrasonography [17,34,35]. Endothelial dysfunction was observed in both long-standing RA patients [36] and young RA patients with low disease activity and without traditional CV risk factors [37].

Persistent endothelial dysfunction predisposes to organic damage of the vascular wall, phenomenon that can be detectable by an increased carotid intima–media thickness (cIMT) [9,38] or by the presence of carotid plaques [39,40] (both assessed by carotid ultrasonography). cIMT corresponds to the width of the vessel intima and media, which consists of endothelium, connective tissue and smooth muscle and is also the site of lipid deposition and plaque formation [41]. A meta-analysis encompassing several population based studies has revealed increased cIMT values in RA patients when compared with non-rheumatic population [42]. Interestingly, as observed in the general population, abnormally high values of cIMT (greater than 0.90 mm) have been found to predict the development of CV events in patients with RA after 5 years of follow-up [22]. Carotid plaque (defined as a focal protrusion in the lumen at least cIMT > 1.5 mm, protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching >0.5 mm in the accessible extracranial carotid tree [43]) has also been described to be an excellent predictor of future CV events in RA [23]. In fact, a 2.5 increased risk of CV events among RA patients with unilateral carotid plaques, and 4.3 among those with bilateral carotid plaques have been reported [23].

A good correlation between the assessment of endothelial function by FMD and the presence of abnormally increased cIMT was observed in RA patients with long disease duration [44].

Finally, besides studies aimed to determine the presence of functional or morphological atherosclerotic changes [45], other non-invasive surrogate markers of CV disease, such as the pulse wave velocity to determine the velocity at which the arterial pulse propagates, which is used clinically as a measure of arterial stiffness hand has a strong correlation with CV events and all-cause mortality in the general population have been found useful in the assessment of CV disease in patients with RA [46].

3. Genes and CV disease in RA

Different studies indicate that genetics plays an important role in the development of CV disease in patients with RA. Most of these studies were conducted by candidate genes strategy in which a specific polymorphism or a set of genetic variants within certain loci were genotyped. These polymorphisms were selected according to their potential biological function or the location in a region previously reported as associated with disease susceptibility or severity. Overall, the result of these studies supports the claim that the genetic component implicated in the development of CV disease in RA is complex, probably the result of gene–gene interactions modulated by environmental factors in which the specific role of a single gene is small. A summary of the main studies addressing the genetic influence in the risk of subclinical atherosclerosis and CV disease in RA is summarized in Table 1.

3.1. Human leukocyte antigen (HLA) and related genes

HLA region includes a group of genes located in the chromosome 6 (6p21) that encode the most polymorphic human proteins, the class I and class II antigen-presenting molecules [47]. Accordingly, HLA is the main genetic factor implicated in inflammatory immune-mediated pathologies, being associated with more diseases than any other region of the human genome [47]. With respect to RA, *HLA-DRB1* gene, especially the *HLA-DRB1*04* shared epitope (SE) alleles, is considered as a risk factor for RA, not only regarding disease susceptibility but also for its implication in the development of CV disease [19]. RA patients carrying 2 copies of the SE exhibit approximately 2-fold increase in mortality due to CV events [19,48], mainly from ischemic heart disease [49]. When specific SE genotypes were analyzed, the *HLA-DRB1*01/*04* combination seems to confer the highest CV risk [19,48,49]. A relationship between *HLA-DRB1* and subclinical atherosclerosis in RA patients has also been demonstrated. In this context, *HLA-DRB1*0404* was associated with endothelial dysfunction [36,50] and with the presence of carotid plaques [51].

HLA-II gene expression is transcriptionally regulated by class II transcriptional activator (CIITA) [52]. This protein acts as a platform for the assembly of various transcription factors to differentially regulate a number of other genes (such as those that codify collagen, cathepsin E, interleukin (IL)-4 and IL-10) [53] and, also, plays a crucial role in atherosclerotic plaque development and complication [53]. This molecule is encoded by *MHC2TA* gene and two genetic variants located in the gene, rs3087456 (−168A>G) and rs4774 (+1614G>C, Gly500Ala), were tested to establish their implication in the development of CV disease in RA. However, no relationship between each polymorphism evaluated individually or in combination conforming haplotypes and clinical CV events or subclinical atherosclerosis was disclosed [54].

3.2. TNF superfamily genes

TNF superfamily cytokines are a group of proteins that activates the nuclear factor-κB (NF-κB) and mitogen activated protein (MAP) kinase signaling pathways [55]. Among them, the potential role of TNF-α, TNF-β, OPG and CD40-CD40L binding in the development of CV disease in RA patients has been evaluated [24,56–60].

TNF-α is a cytokine produced essentially by activated macrophages, although it can be produced by many other cell types [55]. This protein is involved in systemic inflammation, acute phase response and also, in the pathogenesis of a large number of human diseases, including RA [61]. A relevant role of TNF-α in atherosclerosis has also been postulated [62]. *TNFA* genetic variants, mainly *TNFA* rs1800629 (located at *TNFA* promoter), have been proposed as risk factors for autoimmune diseases [63]. In particular, the mutant A allele of *TNFA* rs1800629 has been related to a higher predisposition to CV complications in those RA patients carrying at least a copy of the rheumatoid SE [24]. The implication of another *TNFA* genetic variant in the risk of CV disease in RA, rs1799964, was also evaluated. Although a relationship between rs1799964 polymorphism with a more pro-atherogenic lipid profile was described, no association of this polymorphism with CV events was found [56].

TNF-β or lymphotoxin α (LTA), a cytokine produced by T-helper 1 type T-cells, is best known for its role in the development of lymphoid organs [64]. This protein also induces vascular endothelial cells to change their surface adhesion molecules to allow phagocytic cells to bind to them and, in consequence, is implicated in the early stages of the vascular inflammatory process [65]. In addition, peripheral TNF-β levels showed a correlation with plaque size in mice models [66]. Following these observations, the potential role of a *LTA* genetic variant (rs909253 252A>G) in the increased CV risk observed in RA patients was assessed [57]. Interestingly, a relationship between the 252GG mutant genotype and a higher risk of myocardial infarction was disclosed [57].

A well-known member of the TNF receptor superfamily that plays a central role in bone remodeling is osteoprotegerin (OPG) [67,68]. This molecule has been associated with increased risk of atherosclerotic disease in the general population [69]. The *OPG* human gene is affected by genetic polymorphisms with functional consequences on CV disease and bone metabolism [70,71]. Particularly, *OPG* rs2073617, *OPG* rs2073618 and *OPG* rs3134069 (located in 5´UTR region, exon 1 and promoter region, respectively) have been related to atherosclerosis and risk of cerebrovascular disease in non-rheumatic individuals [72,73]. *OPG* rs3134063 (genetic variant in complete linkage disequilibrium with rs2073617) as well as *OPG* rs2073618 and *OPG* rs3134069 were tested to determine their influence in the risk of CV disease of patients with RA [58]. The result of this assessment revealed that anti-cyclic citrullinated peptide (anti-CCP) antibody-negative RA patients who carried the *OPG* rs2073618GG genotype had a lower risk of developing cerebrovascular complications [58]. Additionally, a protective effect of the *OPG* CGA haplotype (that carries the *OPG* rs2073618G allele) against the risk of cerebrovascular events in the subgroup of RA patients who were anti-CCP antibody-negative was found [58].

Table 1
Genetic association studies in CV disease in patients with RA.

Gene	CV variable analyzed	Results
HLA-DRB1	-CV mortality, CV events	-**0404* ↑ CV events and mortality [19]. 2 copies of the SE are related to higher CV mortality [19,48], mainly IHD [49].**01/04* offers the highest CV risk [19,48,49].
	-FMD	-**0404* ↓ FMD [36,50].
	-FMD, cIMT, carotid plaques	-**0404* ↑carotid plaques [51].
MHC2TA	-CV events, FMD, cIMT	-No association of rs3087456 and rs4774 [54].
TNFA	-CV events, FMD, cIMT	-rs1800629A mutant allele ↑ CV complications in patients carrying at least a copy of the SE [24].
	-Atherogenic measures	-rs1799964C mutant allele ↑ pro-atherogenic lipid profile [56].
LTA	-CV events	-rs909253GG mutant genotype ↑MI risk [57].
OPG	-CV events	-Protective effect of CGA haplotype against CVA in anti-CCP negative patients [58].
CD40	-ATM	-rs1535045 and rs3765459 are related to CV disease [59].
	-CV events, FMD, cIMT	-rs1535045T mutant allele ↓ cIMT. No association of rs1883832 and rs4810485 [60].
CD40L	-CV events, FMD, cIMT	-No association of rs3092952 and rs3092920 [60].
IL6	-CV disease	-rs1800795C mutant allele ↑ the CV risk [76].
	-FMD	-rs1800795GG genotype ↓ FMD [77].
	-CV events	-No association of rs1800795, rs2069827 and rs2069840 [78].
IL6R	-CV events, FMD, cIMT	-No association of rs2228145 [82].
IL6ST	-CV events, FMD, cIMT	-No association of rs2228044 [82].
IFN-ϒ	-CV events, FMD, cIMT, carotid plaques	-No association of rs2430561 [83].
IRF5	-CV events	-Protective effect of rs2004640GG, rs10954213GG and GTG haplotype against CV events [92].
JAK3	-CV events, cIMT, carotid plaques	-No association of rs3212780 and rs3212752 [95].
IL33	-cIMT	-Protective effect of rs3939286T mutant allele. No association of rs7025417 and rs7044343 [103].
IL1RL1	-cIMT	-No association of rs2058660, rs2310173, rs13015714 [103].
NFKB1	-CV events	-*NFKB1*–94 (rs28362491) deletion/deletion ↑ CV risk [25].
TGFB1	-CV events	-rs1800470TC genotype and smoking combination ↑ IHD and MI [108].
SMAD3	-CV events	-rs17228212C mutant allele ↓ CVA risk and subclinical ATS in anti-CCP negative patients [118].
CCR5	-CV events, FMD, cIMT	-Carriers of *CCR5Δ32* deletion showed ↑ FMD [119].
MIF	-CV events	-No association of −173 and -794 [120,121].
	-FMD, cIMT	-No association of −173 [120].
ADIPOQ	-CV events, FMD, cIMT	-No association of rs266729 and rs1501299 [150].
LEP	-CV events, FMD, cIMT	-No association of rs2167270 [157].
RETN	-CV events, FMD, cIMT	-No association of rs1862513 [165].
NAMPT	-CV events, FMD, cIMT	-No association of rs9770242 and rs59744560 [170].
PON1	-Carotid plaques	-rs662RR mutant genotype ↓ carotid plaques [179].
	-cIMT, carotid plaques	-No association of rs662 [180].
	-CV disease	-Anti-HDL antibodies may be pivotal players in the link between *PON1* and CV disease [181].
VDR	-Carotid plaques	-↑ carotid plaques frequency in patients who carried the GATG haplotype [186].
VEGFA	-CV events, FMD, cIMT	-No association of rs2010963 and rs1570360 [199].
NOS	-CV events	-Interaction between *NOS* and *HLA-DRB1* ↑ CV events risk [209].
TLR4	-CV events, FMD, cIMT	-No association of rs4986790 [225].
CARD8	-CV events, cIMT, carotid plaques	-No association of rs2043211 [229].
MTHFR	-CV events, FMD	-1298C mutant allele ↑ CV events risk (after 5 and 10 years of follow-up) and ↓ FMD. No association of C677T [235].
	-IHD	-↓ *MTHFR* expression in IHD [236].
MSRA	-CV events	-rs10903323A mutant allele ↑ CV events (mainly IHD) [239].
GHSR	-CV events, FMD, cIMT	-No association of rs509035, rs512692 and rs2922126 [245].
ACP1	-CV events	-rs11553742T mutant allele and *ACP1*C* haplotype ↑ CV events. No association of rs10167992 and rs3828329 [253].
PTPN22	-CV events, FMD, cIMT	-No association of rs2476601 [261].
TRAF1/C5	-CV events, FMD, cIMT	-No association of rs10818488 [261].
	-CV mortality	-No association of rs10818488 [262].
STAT4	-CV events, FMD, cIMT	-No association of rs7574865 [261].
PIK3CG	-CV events, cIMT, carotid plaques	-No association of rs17398575 [264].
EDNRA	-CV events, cIMT, carotid plaques	-No association of rs1878406 [264].
ABO	-CV events, cIMT, carotid plaques	-No association of rs579459 [264].
	-CV events	-No association of rs579459 [266].
PPAP2B	-CV events, cIMT, carotid plaques	-No association of rs17114036 [264].
	-CV events	-No association of rs17114036 [266].
ADAMTS7	-CV events, cIMT, carotid plaques	-No association of rs3825807 [264].
	-CV events	-No association of rs3825807 [266].
PCSK9	-CV events	-No association of rs11206510 [266].
WDR12	-CV events	-No association of rs6725887 [266].
MRAS	-CV events	-No association of rs2306374 [266].
LPA	-CV events	-No association of rs3798220 [266].
MRPS6	-CV events	-No association of rs9982601 [266].
ANKS1A	-CV events	-No association of rs17609940 [266].
TCF21	-CV events	-No association of rs12190287 [266].
CYP17A1-CNNM2-NT5C2	-CV events	-No association of rs12413409 [266].
HHIPL1	-CV events	-No association of rs2895811 [266].
SMG6-SRR	-CV events	-No association of rs216172 [266].
RASD1-SMCR3-PEMT	-CV events	-No association of rs12936587 [266].

Table 1 (*continued*)

Gene	CV variable analyzed	Results
UBE2Z-GIP-ATP5G1-SNF8	-CV events	-No association of rs46522 [266].
PSRC1- CELSR2- SORT1	-FMD	-rs599839G mutant allele ↓ FMD [268].
ZC3HC1	-cIMT	-rs11556924T mutant allele ↑ cIMT values [267].
MIA3	-CV events	-No association of rs17465637 in UK patients [266].
	-CV events, FMD, cIMT, carotid plaques	-rs17465637A allele is related to CV events risk in dyslipidemic Spanish patients [269].
ZNF259-APOA5-A4-C3-A1	-CV events	-No association of rs964184 in UK patients [266].
	-CV events	-rs964184G mutant allele ↑CV events in Spanish patients [271].
CXCL12	-CV events	-rs1746048T mutant allele ↑ CV events in UK patients [266].
	-CV events, FMD, cIMT	-No association of rs1746048 in Spanish patients [270].

CV: cardiovascular; RA: rheumatoid arthritis; *HLA: Human leukocyte antigen*; SE: shared epitope; IHD: ischaemic heart disease; FMD: endothelial dependent vasodilation; cIMT: carotid intima–media thickness; *MHC2TA: class II major histocompatibility complex transactivator*; *TNFA: tumor necrosis factor alpha, LTA: lymphotoxin alpha;* MI: myocardial infarction; *OPG: osteoprotegerin;* CVA: cerebrovascular accident; anti-CCP antibodies: anti-cyclic citrullinated peptide antibodies; ATM: atherothrombotic manifestations; *CD40L: CD40 ligand; IL6: interleukin 6; IL6R: interleukin 6 receptor; IL6ST: interleukin 6 Signal Transducer; IFN-ϒ: interferon-gamma; IRF5: interferon regulatory factor 5; JAK3: janus kinase 3; IL33: interleukin 33; IL1RL1: interleukin 1 receptor-like 1; NFKB1: factor nuclear NF-kappa-B; TGFB1: transforming growth factor beta 1;* ATS: atherosclerosis; *CCR5: C-C chemokine receptor type 5; MIF: macrophage migration inhibitory factor; ADIPOQ: adiponectin; LEP: leptin; RETN: resistin; NAMPT: nicotinamide phosphoribosyltransferase; PON1: paraoxonase 1;* HDL: high-density lipoproteins; *VDR: vitamin D receptor; VEGFA: vascular endothelial growth factor A; NOS: nitric oxide synthase; TLR4: toll-like receptor 4; CARD8: caspase recruitment domain family member 8; MTHFR: methylenetetrahydrofolate reductase; MSRA: methionine sulfoxide reductase A; GHSR: hormone secretagogue receptor; ACP1: acid phosphatase 1; PTPN22: protein tyrosine phosphatase non-Receptor type 22; TRAF1/C5: TNF receptor associated factor 1/complement component 5; STAT4: signal transducer and activator of transcription 4; PIK3CG: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma; EDNRA: endothelin receptor type A; ABO: histo-blood group ABO system transferase; PPAP2B: phosphatidic acid phosphatase type 2B; ADAMTS7: metallopeptidase with thrombospondin type 1 motif 7; PCSK9: proprotein convertase subtilisin/kexin type 9; WDR12: WD repeat domain 12; MRAS: muscle RAS oncogene homolog; LPA: lipoprotein(a); MRPS6: mitochondrial ribosomal protein S6; ANKS1A: ankyrin repeat and sterile alpha motif domain containing 1A; TCF21: Transcription Factor 21; CYP17A1-CNNM2-NT5C2: cytochrome P450 family 17 subfamily A member 1-cyclin and CBS domain divalent metal cation transport mediator 2-5′-nucleotidase, cytosolic II; HHIPL1: hedgehog interacting protein-like 1; SMG6-SRR: SMG6 nonsense mediated mRNA decay factor- Serine racemase; RASD1-SMCR3-PEMT: RAS, dexamethasone-induced 1-Smith–Magenis syndrome chromosome region candidate 3-phosphatidylethanolamine N-methyltransferase; UBE2Z-GIP-ATP5G1-SNF8: ubiquitin conjugating enzyme E2 Z-gastric inhibitory polypeptide-ATP synthase, H + transporting, mitochondrial Fo complex subunit C1 (subunit 9)-SNF8, ESCRT-II complex subunit; PSRC1- CELSR2- SORT1: proline/serine-rich coiled-coil 1-cadherin EGF LAG seven-pass G-type receptor 2-sortilin 1; ZC3HC1: zinc finger C3HC-type containing 1; MIA3: melanoma inhibitory activity family member 3; ZNF259-APOA5-A4-C3-A1: zinc finger protein 259-apolipoprotein A-V-IV-C-III-A-I; CXCL12: C-X-C motif chemokine ligand 12.*

CD40-CD40L binding is an essential pathway related to T-B cell interactions that also mediates pro-atherogenic biological responses (expression of cytokines, chemokines, growth factors, matrix metalloproteinases) [55]. Several polymorphisms located both in *CD40* and *CD40L* genes were evaluated according to the development of CV disease in RA patients [59,60]. Regarding *CD40*, the rs3765459 polymorphism was found to be a genetic variant associated with CV events [59] whereas the *CD40* rs1535045 variant was associated with CV events [59] and subclinical atherosclerosis (an assessment by carotid ultrasound disclosed association with cIMT) [60]. However, neither *CD40* rs1883832 nor *CD40* rs4810485 polymorphisms were found to be associated with CV events or subclinical atherosclerosis in RA [60]. Regarding *CD40L*, no association was observed when *CD40L* rs3092952 and *CD40L* rs3092920 polymorphisms were assessed for the presence of CV events or subclinical atherosclerosis in patients with RA [60].

3.3. Cytokines and related genes

Cytokines constitute a broad category of small proteins that regulate fundamental biological processes including body growth, adiposity, and hematopoiesis.

One of the most relevant pro-inflammatory cytokines is the IL-6. This pleiotropic protein is produced by different cells (monocytes, endothelial cells, fibroblasts and activated T lymphocytes) [74] and is essential in adaptive immunity [75]. Besides, this molecule also acts in the innate immune response contributing to the systemic effects of inflammation [75]. The potential association between *IL6* gene and the development of CV disease in RA has been tested by several authors with apparently contradictory results [76–78]. With respect to this, a genetic variant located in the 5′ flanking region at position −174 (G>C; rs1800795) was associated with higher risk of CV disease as well as an increased endothelial dysfunction in a relatively small cohort of British [76] and Spanish [77] RA patients, respectively. However, when assessed in a larger cohort of patients in whom the major variability of the *IL6* gene was covered by tagging, no association between *IL6* -174 rs1800795 and CV events was found [78]. It was also the case for another two *IL6* polymorphisms (rs2069827 and rs2069840) [78].

Both IL-6 levels and functions seem to be partially controlled by its receptor [79]. In this sense, IL-6 receptor is a protein complex consisting of an IL-6 receptor subunit (IL6R) and IL-6 signal transducer Glycoprotein 130 (also called IL-6ST). A study performed in a large cohort of Spanish RA patients evaluated the influence of the *IL6R* rs2228145 (that alters IL6R levels [80]) and *IL6ST* rs2228044 (related to myocardial infarction in a hypertensive population [81]) in the risk of CV disease [82]. However, the results derived from this study revealed a lack of association between these two genetic variants and CV events or endothelial dysfunction in RA [82].

Due to the association of the mean values of C-reactive protein (CRP) in long-standing RA patients with the presence of subclinical atherosclerosis [18], CV events and CV mortality [19], our group has set up a study to determine the potential influence of *CRP* gene polymorphisms in the risk of CV disease in patients with RA. For this purpose, 3 *CRP* polymorphisms (rs1417938, rs1800947, rs1205) selected by tagging and 9 genetic variants (*HNF1A, LEPR, GCKR, NLRP3, IL1F10, PPP1R3B, ASCL1, HNF4A* and *SALL1*) related to serum CRP levels in non-rheumatic Caucasians have been genotyped by TaqMan assays in a total of 2,313 Spanish RA patients. However, unpublished preliminary observations suggest that there is no association between these CRP serum level-related genetic variants and the presence of subclinical atherosclerosis or CV events in patients with RA (unpublished data).

Interferon gamma (IFN-ϒ) is a pleiotropic cytokine member of the type II class of interferons involved in innate and adaptive responses [83] that also plays a relevant role in atherosclerosis and plaque disruption (by enhancing expression of adhesion molecules on endothelial cells) [84]. This molecule recruits macrophages and T cells into the plaque, contributing to the production of reactive oxygen species, inhibiting collagen production, stimulating matrix metalloproteinases, and inducing tissue factors expression [6,85,86]. Taking into account all these considerations, we studied the potential implication of the functional *IFNG* rs2430561 polymorphism in the risk of CV disease in RA [83]. However, no association of *IFNG* rs2430561 with CV events or subclinical atherosclerosis was observed in patients with RA [83].

Type I IFN gene transcription is regulated by a molecule termed interferon regulatory factor 5 (IRF5) [87,88] and, therefore, this protein is critical for the production of pro-inflammatory cytokines [89]. Furthermore, IRF5 acts as a molecular switch that controls inflammatory mechanisms mediated by macrophage cells [89]. Some genetic variants located in *IRF5* have been proposed as essential players in the development of rheumatic diseases [90,91]. Particularly, *IRF5* rs2070197, *IRF5*

rs2004640 and *IRF5* rs10954213 were found to be independently associated with these inflammatory disorders. Regarding the development of CV disease in RA, a recent study has shown a protective effect of both the *IRF5* rs2004640GG and the *IRF5* rs10954213GG genotypes against the risk of CV events [92]. Additionally, when *IRF5* rs2070197, *IRF5* rs2004640 and *IRF5* rs10954213 were analyzed together, a protective effect of the GTG haplotype in the development of CV events in patients with RA was also found [92].

Most ILs (such as IL-6), IFNs and colony-stimulating factor (CSFs) mediate their effects through the Janus kinase (JAK)-signal transducers and activators of transcription (STAT) pathway [55]. Among them, JAK3 is a member of the JAK family protein which associates with the common γ (γc) chain [93]. JAK3 has limited tissue expression and its only meaningful biological function is restricted to immune cells [55]. A relationship between *JAK3* genetic variants and inflammatory disorders, including the development of CV events in incident dialysis patients, was reported [94]. However, we could not find an association of 2 genetic *JAK3* variants, *JAK3* rs3212780 and *JAK3* rs3212752, with the risk of CV disease in Spanish individuals with RA [95].

Another recently characterized pro-inflammatory cytokine that belongs to the IL-1 family is the IL-33 [96]. This molecule exerts its biological function by interacting with its receptor (IL-1 receptor like 1 (IL-1RL1)) and co-receptor (IL-1 receptor accessory protein (IL-1RAcP)). The IL-33-IL-1RL1 binding mediates relevant immunomodulatory functions [96]. Regarding RA, an association between baseline detectable IL-33 concentrations and the development of severe subclinical atherosclerosis was described [97]. Because of that, we analyzed the potential influence of the *IL33* rs3939286, *IL33* rs7025417, *IL33* rs7044343, *IL1RL1* rs2058660, *IL1RL1* rs2310173 and *IL1RL1* rs13015714 polymorphisms, which were described to be associated with several inflammatory diseases [98–102], on the risk of CV disease in RA [103]. Interestingly, we disclosed a potential protective effect of the mutant *IL33* rs3939286T allele in the risk of subclinical atherosclerosis in patients with RA [103].

IL-1 (including IL-33) and TNF family members activate NF-kB signaling pathway [55]. The latter plays a central role in inflammation through the regulation of genes encoding pro-inflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes such as inducible nitric oxide synthase [104]. Because of that, the inappropriate activation of NF-kB predisposes to the development of a variety of human diseases and pathologic conditions [105,106]. With respect to this, the *NFKB1* −94 insertion/deletion ATTG (rs28362491) promoter polymorphism, that shows functional effects on the transcription of *NFKB1,* has been related to several immune-mediated disorders [107]. In keeping with that, an association between this genetic variant (specifically the *NFKB1* −94 deletion/deletion genotype) and a higher risk of CV events in RA patients was found [25].

Transforming growth factor beta 1 (TGF-β1) is a multifunctional cytokine belonging to the TGF-β superfamily implicated in the modulation of both immunity and inflammation [108]. The role of TGF-β1 in the pathogenesis of atherosclerosis has long been the subject of debate [109,110]. Inhibition of endogenous TGF-β signaling favors the development of atherosclerotic lesions [109]. However, a pro-atherogenic role of TGF-β1 is also suspected since it is able to promote fibrosis and to inhibit endothelial regeneration [110]. Regarding these observations, some authors have analyzed whether variations in the *TGFB1* gene could be involved in the development of CV disease in RA patients [108]. For this purpose, *TGFB1*-509 C/T (rs1800469, in the promoter region), +868 T/C (rs1800470, in exon 1) and +913 G/C (rs1800471, in exon 1) were evaluated [108]. The result of this assessment yielded that the combination of *TGFB1* rs1800470TC genotype and smoking habit was associated with a higher risk of CV events (especially ischemic heart disease and myocardial infarction) [108].

TGF-β superfamily cytokines mediate their effects by activating signaling proteins of the SMAD family [55]. These molecules are intracellular proteins that transduce extracellular signals to the nucleus where they activate downstream gene transcription [111–113]. Among them, SMAD3 has an essential role in downregulating T-cells and increasing regulatory T-cells differentiation [114]. Besides, SMAD3 expression has been found in human plaques, mainly in macrophages of fibro-fatty lesions and in smooth muscle cells of fibrous caps [115]. *SMAD3* gene has been implicated in different immune-mediated disorders [116,117]. In this regard, the *SMAD3* rs17228212 genetic variant (the mutant C allele) was associated with a lower risk for cerebrovascular accidents and less severe subclinical atherosclerosis in patients with RA who were negative for anti-CCP antibodies [118].

3.4. Chemokines genes

Chemokines are a family of small cytokines that have the ability to induce directed chemotaxis in nearby responsive cells [55]. These molecules are especially important in the regulation of inflammatory and immune responses and have crucial functions in controlling both innate and adaptive immunity [55]. Because of that, the influence of these proteins in the CV risk associated with RA was evaluated by different authors [119–121].

CCR5 (C-C chemokine receptor type 5) is a protein located on the surface of white blood cells that is involved in the immune response as it acts as a receptor for chemokines. Additionally, a potential pro-inflammatory effect of this molecule in both RA pathogenesis and atherosclerosis has been proposed [122]. The implication of the *CCR5Δ32* rs333 polymorphism (defined by a 32-bp deletion that leads to a truncated nonfunctional receptor [123]) has been studied in different diseases. It is known that in individuals who are homozygous for this deletion CCR5 is absent from the cell surface [124] whereas heterozygous individuals express 20% to 30% of the CCR5 levels observed in wild-type individuals [125]. Although the role of this genetic variant in both the development of CV disease [126–130] and RA pathogenesis [131–133] has generated contradictory results, a study in Spanish patients with RA suggested an implication of this polymorphism with CV disease [119]. In this regard, carriers of the *CCR5Δ32* deletion showed higher FMD values than the remaining patients (7.03% ± 6.61% versus 5.51% ± 4.66%). This difference was statistically significant when analysis of covariance was performed ($P = 0.024$). Because of that, these results speak in favor of a protective effect of *CCR5Δ32* rs333 against the development of endothelial dysfunction in patients with RA [119].

The macrophage migration inhibitory factor (MIF) is a predominantly macrophage-derived cytokine, which has been reported to contribute to the development of CV disease [134]. Alternatively, MIF displays chemokine-like functions and acts as a major regulator of inflammatory cell recruitment and atherogenesis [135]. Two *MIF* polymorphisms previously related to higher plasma MIF levels (a tetra-nucleotide repeat element starting at position −794 [$CATT_{5-8}$] and a single-nucleotide polymorphism at position -173 [G/C]) were tested to determine a potential association with CV disease in RA [120,121]. However, neither of these genetic variants was associated with the development of CV events [120,121]. In addition, no association of the *MIF*-173 with subclinical atherosclerosis, studied by the assessment of cIMT and FMD values, was found [120].

3.5. Adipokines genes

The term adipokines is referred to a specific group of immune mediator proteins secreted by the adipose tissue [136]. These molecules influence metabolic processes such as glucose and lipid metabolism [137] and exert potent modulatory actions on target tissues and cells involved in rheumatic diseases [138,139].

Among these molecules is adiponectin. This adipokine is secreted by adipocytes and circulates in the blood in large amounts and constitutes approximately 0.01% of the total plasma proteins [140]. Adiponectin increases fatty acid oxidation and reduces the synthesis of glucose in the liver and other tissues [141]. Several studies have revealed that adiponectin circulating levels inversely correlate with adiposity [142,

143]. In this regard, in patients with severe RA, high-grade inflammation was independently and negatively correlated with circulating adiponectin concentrations whereas low adiponectin levels clustered with metabolic syndrome (MetS) features that reportedly contribute to atherogenesis in RA [143]. These findings suggest that this adipokine may exert a protective function against CV disease and obesity. Interestingly, *ADIPOQ* rs266729 and *ADIPOQ* rs1501299 gene variants have been found associated with CV disease in non-rheumatic individuals [144–149]. Taking into account these considerations, these two *ADIPOQ* gene variants were tested in patients with RA. However, no association with CV events or subclinical atherosclerosis was observed [150].

Leptin is another adipokine mainly produced by adipocytes [136, 140] with a crucial role in body weight regulation by inhibiting food intake and stimulating energy expenditure [151]. This protein also induces the production of pro-inflammatory cytokines such as IL-6, IL-12, and TNF-α by monocytes and macrophages [152] while it suppresses the production of IL-4 and anti-inflammatory cytokines [153]. In patients with RA undergoing anti-TNF therapy, circulating leptin levels constituted a manifestation of adiposity [154]. In this regard, a strong association between leptin serum levels and body mass index was observed in RA patients with severe disease [154]. Since a genetic variant located in *LEP* gene (*LEP* rs2167270) was proposed as a relevant signal involved in the leptin levels [155] and obesity [156], García-Bermúdez et al. analyzed the potential association between this polymorphism and the development of CV disease in RA [157]. However, no significant association was observed with CV events or subclinical atherosclerosis (evaluated by cIMT assessment and FMD studies) [157].

Another adipocyte-derived mediator that plays an important role in inflammation [136,158] is a protein called resistin. Although this molecule can be detected at very low levels in human adipose tissue, it is mainly found in peripheral blood mononuclear cells [159]. Resistin has been found to be up-regulated by some cytokines such as TNF-α and IL-6 [160] and has been proposed as an important molecule in NF-κB activation and cytokine production [161]. A significant association between the mean erythrocyte sedimentation rate (ESR) and CRP from disease diagnosis and ESR, CRP and platelet count at the time of the study and Resistin levels in patients with RA refractory to conventional disease-modifying anti-rheumatic drugs that required biologic therapy was observed [162]. Interestingly, a polymorphism located at the *RETN* gene promoter (*RETN* rs1862513) was found associated with a higher risk of cerebrovascular disease in patients with type 2 diabetes mellitus [163,164]. Based on these findings, this genetic variant was tested for CV risk in patients with RA. However, no association between *RETN* rs1862513 and CV events or subclinical atherosclerosis was found in patients with RA [165].

Finally, visfatin is an insulin-mimetic adipokine with ubiquitous expression that has also been associated with inflammation [136,166]. This adipokine correlates with visceral fat [167] and has been described as an immunomodulatory molecule [168,169]. Visfatin can induce monocytes to produce pro-inflammatory cytokines [168]. Likewise, this adipokine has inflammatory and destructive functions promoting joint damage in patients with RA [169]. Polymorphisms located in *NAMPT* (gene that encodes visfatin) were assessed to determine their potential association with CV disease in patients with RA [170]. In this context, two genetic variants (*NAMPT* rs9770242 and *NAMPT* rs59744560) related to IR and a pro-atherogenic lipid profile [171, 172], were tested in a cohort of Caucasian RA patients [170]. However, no significant association between these polymorphisms and clinical CV events or subclinical atherosclerosis was found [170].

3.6. Genes related to lipid metabolism and vitamin D

Endogenous molecules formed because of dyslipidemia, lipid accumulation and oxidative modification of lipids retained in the vessel wall act as danger signals that activate innate immune responses [173] forming the fatty streak, the earliest visible lesion in the development of atherosclerosis [55]. Because of that, molecules involved in lipid metabolism are of main importance in the development of this process and the potential role of gene polymorphisms that influence the expression of these molecules are of potential relevance in terms of the CV risk in patients with RA.

Paraoxonase 1 (PON1) is a high-density lipoprotein (HDL)-associated enzyme that promotes the antioxidant and anti-inflammatory properties of HDL [174–176]. Reduced activity of PON1 has been associated with CV events in the general population [177] and level variation of this molecule is mostly influenced by the *PON1* Q192R (rs662) polymorphism [178]. However, the involvement of this polymorphism in the development of CV disease in RA is controversial [179,180]. Although a relationship between the mutant *PON1* 192RR genotype and a decreased risk of carotid plaque has been suggested in a small cohort of Caucasian patients [179], this polymorphism was not associated with the presence of subclinical atherosclerosis in a large cohort of Spanish patients with RA [180]. These apparently contradictory results may suggest the implication of other factors related to PON1 activity. In this regard, a recent study has proposed that anti-HDL antibodies may be the pivotal players to understand the link between *PON1* rs662 and CV disease in RA [181].

Vitamin D receptor (VDR) is an intracellular steroid/thyroid hormone receptor expressed in almost all tissues and immune cells [182] that exerts its function by binding with its ligand, vitamin D. The vitamin D/VDR axis affects the transcription of several responsive-genes and also inhibits T-helper 1 and T-helper 17 cell responses, while promoting T-helper 2 and regulatory T cell responses [183]. An association between *VDR* gene variants and immune-mediated conditions was disclosed, being *VDR* GAT (composed of the minor allele of *VDR* rs731236, major allele of *VDR* rs7975232 and minor allele of *VDR* rs1544410) the risk haplotype for coronary artery disease in type-2 diabetes mellitus [184] and obesity [185]. In keeping with these observations, a potential *VDR* association with atherosclerotic disease was observed in patients with RA [186]. In this regard, the *VDR* rs7975232AA genotype was associated with an increased frequency of carotid plaques in patients with RA [186]. Similarly, and more importantly, *VDR* GATG haplotype (who harbors the A allele of *VDR* rs7975232) was more frequently observed in RA patients with carotid plaques [186].

3.7. Neovascularization genes

It is well known that most pro-inflammatory and pro-atherogenic mediators enhance neovessel formation whereas most anti-inflammatory and anti-atherogenic mediators inhibit the neovascularization process [55], a phenomenon of main relevance both in the development and destabilization of atherosclerotic plaques [187,188].

Among pro-angiogenic factors, the vascular endothelial growth factor (VEGF) has been described as a molecule with pro-inflammatory, pro-atherogenic and pro-angiogenic properties [189,190]. This protein causes an increase in the plaque growth, [191,192] exerts different actions in the endothelial cells [193–196] and also stimulates monocytes [197]. Several polymorphisms within the *VEGFA* promoter and 5′UTR region (*VEGFA* rs2010963 (−634 G>C) and *VEGFA* rs1570360 (−1154 G>A)) regulate *VEGFA* expression at the post-transcriptional level [198]. However, no association of these two *VEGFA* polymorphisms with the risk of CV events or the presence of subclinical atherosclerosis was found in patients with RA [199].

3.8. Nitric oxide synthase (NOS) genes

As mentioned above, NO is crucial in the development of atherosclerosis. In physiological conditions, NO acts as an anti-inflammatory molecule, maintaining the vascular wall in a quiescent state, also avoiding cellular proliferation. However, in the presence of inflammation or CV risk factors, the quiescent endothelium can switch to an activated phenotype that leads to the secretion of pro-inflammatory factors and to

the generation of reactive oxygen species [200]. This pathological inflammatory condition also leads to a reduction in the release of NO into the arterial wall, either affecting its synthesis or due to oxidative inactivation of NO [201,202], which further enhances the inflammatory status and maintains the endothelial activated phenotype [200]. NO is produced constitutively by the endothelial (eNOS or NOS3), or neuronal (nNOS or NOS1) synthases, or in higher concentrations by the inducible (iNOS or NOS2) synthases [203]. Different vascular diseases have been associated with functional single-nucleotide polymorphisms in *NOS2A* and *NOS3* [204–206]. In addition, the *NOS2A* (CCTTT)n repeat variations have been related to RA susceptibility [207,208]. *NOS2A* (CCTTT)n polymorphism and *NOS3* genetic variants (−786 and 298Glu/Asp) do not infer a direct risk for CV events in patients with RA [209]. Nevertheless, an association of these genetic variants with CV events was observed in patients with RA who carried the *HLADRB1*0404* allele [209]. These findings support the claim that complex gene-gene interactions may be responsible for the increased risk of CV disease observed in patients with RA.

3.9. Innate immunity genes

The innate immunity is involved in the atherosclerotic disease process, starting from the earliest events of endothelial cell expression of adhesion molecules, chemokine release and monocyte recruitment to the complex cellular interactions in the mature lesion [210–212]. Pattern recognition receptors, including Toll-like receptors (TLRs), play pivotal roles in the development of the atherosclerotic disease [213–216].

TLRs are single, membrane-spanning, non-catalytic receptors usually expressed in sentinel cells such as macrophages and dendritic cells that recognize structurally conserved molecules derived from microbes [217].

TLR4 activation, which depends on bacterial lipopolysaccharides, promotes the production and release of pro-inflammatory cytokines [218]. This protein can directly interfere with the cholesterol metabolism in macrophages [219]. TLR4 has been detected in human carotid and coronary atherosclerotic plaques [220,221]. Interestingly, the *TLR4* rs4986790 (Asp299Gly) polymorphism was associated with a decreased risk of atherosclerosis and acute coronary events in non-rheumatic individuals [222–224]. However, no relationship between this genetic variant and the development of CV disease in patients with RA was observed [225].

The caspase recruitment domain-containing protein 8 (CARD8) is a member of the cytoplasmic IL-1β regulating protein complex (inflammasome), an assembly of proteins with a substantial role in modulating adaptive immune responses [226]. This molecule is also involved in pathways leading to activation of caspases or NF-κB in the context of apoptosis or inflammation, respectively. A *CARD8* polymorphism (rs2043211) that changes cysteine at codon 10 to a premature termination codon (c.30T>A; p.C10X) was associated with both severity and a worse disease course in RA [227,228]. However, no association between *CARD8* rs2043211 and the risk of CV disease was found in patients with RA [229].

3.10. Potential association of other genes with CV disease in RA

A well-characterized enzyme that catalyzes the irreversible reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate (the methyl donor for the conversion of homocysteine to methionine) is the methylene tetrahydrofolate reductase (MTHFR) [230]. Genetic variants located in the *MTHFR* gene (A1298C and C677T) have been related to decreased MTHFR enzyme activity. This situation leads to higher homocysteine plasma levels that are associated with an increased risk of CV disease [231–233]. Moreover, an association of the A1298C polymorphism in the *MTHFR* gene with susceptibility to RA in Southern European individuals was reported [234]. The potential role of these variants in the augmented CV risk observed in RA patients was also assessed [235]. Although no association between *MTHFR* C677T (rs1801133) and CV events or subclinical atherosclerosis was disclosed [235], the mutant C allele of *MTHFR* A1298C (rs1801131) was found to confer an increased risk of CV events (after 5 and 10 years of follow-up) and severe endothelial dysfunction in patients with RA [235]. In keeping with this observation, we have recently observed a decreased *MTHFR* expression in RA patients with ischemic heart disease [236].

The methionine sulfoxide reductase A (MSRA) is a ubiquitous well-conserved enzyme that carries out the enzymatic reduction of methionine sulfoxide to methionine. Its function is the repair of oxidative damage to proteins to restore the biological activity [237]. The *MSRA* gene has been demonstrated to be involved in the pathogenesis of a variety of autoimmune disorders [238]. With respect to RA, *MSRA* rs10903323 polymorphism seems to be implicated in the increased risk to develop CV events, in particular ischemic heart disease [239].

Ghrelin is a peptide predominantly expressed in the stomach [136] that has been considered as a relevant MetS-related biomarker that regulates food intake and growth hormone (GH) expression [240]. In consequence, low levels of this peptide have been observed in obese individuals [241]. This protein also acts as an anti-inflammatory [240,242] and anti-atherogenic [243] molecule through its expression in immune and vascular cells. Genetic polymorphisms located in the *Ghrelin* gene (*GHSR*), *GHSR* rs509035 and *GHSR* rs512692, were associated with ischemic heart disease in non-rheumatic disease individuals [244]. These genetic variants along with the *GHSR* rs2922126 polymorphism, which is located in a putative binding site for a transcriptional factor involved in transcription of matrix metalloproteinase's, were assessed in patients with RA [245]. However, no association of these *GHSR* polymorphisms with CV disease or with subclinical atherosclerosis was found in patients with RA [245].

Acid phosphatase locus 1 (*ACP1*) is a gene that encodes a low molecular weight phosphortyrosine phosphatase implicated in different cell biological functions [246,247]. This protein has been considered a key regulator of signaling pathways in receptor-stimulated immune cells [248], growth factor regulation [249], T-cell development, lymphocyte activation [250] and in the integrin signaling during cellular adhesion [248]. *ACP1* polymorphisms have been associated with susceptibility to several human diseases [246,251] and coronary artery disease [252]. Additionally, the minor allele of *ACP1* rs11553742 as well as the *ACP1*C* haplotype (integrated by *ACP1* rs11553742 minor allele and *ACP1* rs7576247 major allele) was associated with a higher risk of CV events in RA [253]. However, no relationship between both *ACP1* rs10167992 and *ACP1* rs3828329 and CV events or subclinical atherosclerosis was found in RA [253].

PTPN22 (*protein tyrosine phosphatase, non-receptor type 22*) [254–256], *TRAF1* (*TNF receptor associated factor 1*)/*C5* (*complement component 5*) [257] and *STAT4* [258–260] genes are relevant regulators involved in the pathogenesis of RA. Because of that, the potential association of polymorphisms located in these genes and the development of CV disease in RA was also assessed [261,262]. However, neither *PTPN22* rs2476601 nor *STAT4* rs7574865 were found associated with the risk of CV events or subclinical atherosclerosis in a cohort of RA Spanish patients of Caucasian ancestry [261]. It was also the case for the *TRAF1/C5* rs10818488 polymorphism [261]. In keeping with these observations, *TRAF1/C5* rs10818488 was not associated with a higher incidence of mortality due to CV disease in another two Caucasian cohorts [262].

A meta-analysis of subclinical atherosclerosis performed in non-rheumatic Caucasians described some genetic variants as significant signals related to both cIMT and presence of carotid plaques [263]. Following these findings, several studies were conducted to determine whether these polymorphisms could be also implicated in the development of CV disease in patients with RA [264]. However, no association between *PIK3CG* (*phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma*) rs17398575 and *EDNRA* (*endothelin receptor type A*)

rs1878406 and the development of CV events or subclinical atherosclerosis in RA was observed [264].

In line with the above, a large-scale study identified several genetic factors as relevant polymorphisms involved in the development of coronary artery disease in the general population [265]. Based on these findings, several studies addressed the potential role of these polymorphisms in the development of CV disease in RA [264,266–271]. Interestingly, patients with RA carrying the minor allele of *PSRC1* (*proline/serine-rich coiled-coil 1*)-*CELSR2* (*cadherin EGF LAG seven-pass G-type receptor 2*)-*SORT1* (*sortilin 1*) rs599839 showed a higher risk of endothelial dysfunction [268] whereas the *ZC3HC1* (*zinc finger C3HC-type containing 1*) rs11556924T mutant allele was associated with increased cIMT values in patients with RA [267]. Also, the *MIA3* (*melanoma inhibitory activity family member 3*) rs17465637 [269] and *ZNF259-APOA5-A4-C3-A1* rs964184 (*zinc finger protein 259-apolipoprotein A-V-IV-C-III-A-I*) [271] were associated with the development of CV events in Spanish RA patients but not in UK individuals with RA [266]. In contrast, *CXCL12* (*C-X-C motif chemokine ligand 12*) rs1746048 was proposed to be a genetic variant involved in the CV risk of patients with RA from UK [266]. However, no association of this polymorphism with CV events was observed in a large series of Spanish patients with RA [270].

3.11. New strategies for the assessment of the genetic influence of CV disease in RA: high-throughput genotyping techniques

Unlike candidate gene strategy, in high-density polymorphism arrays, hundreds of thousands of probes are arrayed on a small chip allowing for many genetic variants to be interrogated simultaneously. Among them, Immunochip and Genome-Wide Association Studies (GWAS) are large-scale approaches used in the genetic characterization of immune-mediated diseases [272,273]. Immunochip allows a dense analysis of 196,524 single-nucleotide polymorphisms, rare variants, and insertion/deletion polymorphisms, located within 186 known susceptibility loci for autoimmune and inflammatory disorders [274]. Otherwise, GWAS approach is a free-hypothesis genetic method [275] in which hundreds of thousands of single-nucleotide polymorphisms can be analyzed across the whole genome [276].

The use of these techniques in patients with RA has substantially increased the number of established genetic risk factors related to this pathology [90,257,277,278]. However, information specifically focused on CV disease in RA is not available yet. In this regard, the first GWAS and Immunochip studies for CV outcome in RA are underway in a cohort of Spanish patients. Of potential relevance may be the results derived from the assessment of a large series of RA patients in whom information on cIMT and carotid plaques is also available. Data generated in these studies may help to improve our understanding of the genetic bases of this pathology and provide new candidate genetic markers of CV disease in RA.

4. MetS-related biomarkers, adipokines and biomarkers of endothelial cell activation and inflammation and CV disease in RA

MetS represents a cluster of CV risk factors, such as obesity, elevated triglycerides, low levels of HDL-cholesterol, high systolic and diastolic blood pressure and elevated fasting glucose [279] that triggers IR and increased visceral adiposity [280]. This entity has received great attention in the last years due to its contribution to the burden of CV morbidity and mortality [281–283] and its high prevalence in patients with inflammatory rheumatic diseases [282] such as RA [31,32,139,284,285].

The adipose tissue is not only a passive tissue but it is also considered a dynamic organ that releases adipokines [31,137,285,286] and some pro-inflammatory cytokines. In this regard, visceral fat accumulation associated with adipokine dysregulation affects subclinical atherosclerosis [287], being particularly related to atherosclerotic plaque development and disruption. Additionally, the release of pro-inflammatory cytokines together with MetS factors leads to endothelial cell activation and, consequently, to the expression of endothelial adhesion molecules that recruit inflammatory cells to the vascular wall, which generates reactive oxygen species [200].

Much effort has recently been focused on the potential influence of MetS-related biomarkers, adipokines and biomarkers of endothelial cell activation and inflammation in the development of CV disease in patients with RA. In this sense, results of these studies indicate these molecules as relevant biomarkers of CV outcome in RA. A review of these studies is discussed below. Furthermore, a summary is shown in Table 2.

4.1. MetS-related biomarkers

As mentioned before, IL-6 is a pleiotropic cytokine with a crucial role in pro-inflammatory responses. However, it is important to highlight that this protein also plays a direct role in mediating IR [288]. Specifically, IL-6 acts by inhibiting insulin receptor signal transduction and insulin action [288]. In this regard, elevated IL-6 serum concentration has been proposed as an essential factor related to pathologies associated with IR [289,290]. Based on this information, the potential influence of IL-6

Table 2
Studies on MetS-related biomarkers, adipokines and biomarkers of endothelial cell activation and inflammation in CV disease in patients with RA.

Molecule	Results
IL-6	-Predictor of endothelial dysfunction [291]. -↓ IL-6 serum levels ↓ endothelial cell activation [292].
Ghrelin	-↑ Ghrelin serum levels ↓ endothelial cell activation [293]. -No association with cIMT [294].
Adiponectin	-↑ Adiponectina serum levels ↑ blood pressure and ↓ glucose in black and white patients. ↑ adiponectin serum levels ↑favorable lipid profile in black patients. ↑ adiponectin serum levels ↑endothelial activation in white patients [295]. -↓ Adiponectin serum levels clustered with MetS features and high-grade inflammation [143]. -No association with cIMT [294]. -No association with coronary atherosclerosis [296]. - Adiponectin serum levels are related to ↓ carotid plaque prevalence in patients with abdominal obesity or clinical absent joint damage [297].
Leptin	-↑ Leptin serum levels ↑ BMI [154]. -No association with cIMT [294]. -Interaction with HOMA-IR index [296].
Leptin/adiponectin ratio	-Related to MetS factors. Independent marker for CV risk [298].
Resistin	-↑ resistin serum levels ↑ CRP and ESR [162,299,300]. -No association with cIMT [294]. -No association with coronary atherosclerosis [296]. -↑ Resistin serum levels ↑ endothelial activation [301].
Visfatin	-No association with obesity or MetS [302]. -No association with cIMT [294]. -No association with coronary atherosclerosis [296].
ICAM-1	-No association with cIMT or carotid plaques [307].
ICAM-3	-No association with cIMT or carotid plaques [307].
VCAM-1	-Relationship with cIMT and carotid plaques [291].
P-selectin	-No association with cIMT or carotid plaques [307].
E-selectin	-No association with cIMT or carotid plaques [307].
Angpt-2	-↑ Angpt-2 serum levels ↑ CV events [308,311].
OPG	-↑ OPG serum levels ↑ carotid plaques [314,315]. -↑ OPG serum levels ↑ endothelial cell activation [315]. -↑ OPG serum levels ↑ CV events [316].
TRAIL	-↓TRAIL serum levels ↑ HF [325].
ADMA	-↑ADMA serum levels are related to markers of active inflammation and oxidative stress [335].
SDMA	-↑SDMA serum levels ↑IS and disease activity score [326]. -No association with traditional CV disease risk factors and markers of inflammation [340].

MetS: metabolic syndrome; CV: cardiovascular; RA: rheumatoid arthritis; IL: interleukin; cIMT: carotid intima–media thickness; BMI: body mass index; HOMA-IR: homeostatic model assessment-insulin resistance; CRP: C-Reactive protein; ESR: erythrocyte sedimentation rate; ICAM: intercellular adhesion molecule; VCAM: vascular endothelial adhesion molecule; Angpt: angiopoietin; OPG: Osteoprotegerin; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; HF: heart failure; ADMA: asymmetric dimethylarginine; SDMA: Symmetric dimethylarginine; IS: insulin sensitivity.

serum levels in the development of CV disease in patients with RA has also been assessed. In this respect, Dessein et al. have described that IL-6 is independently predictive of endothelial dysfunction [291] and, therefore, a reduction in its serum levels leads to decreased endothelial cell activation in patients with RA [292].

Since ghrelin is an anti-inflammatory molecule and low levels of ghrelin may be associated with obesity [241], several studies have been focused on the potential role of this molecule in the development of CV events and subclinical atherosclerosis in RA. In this regard, in a series of RA patients with severe disease undergoing anti-TNF-α infliximab therapy a rapid increase of serum ghrelin levels was observed following a single administration of this biologic agent [293]. Additionally, increased ghrelin circulating concentration was associated with decreased endothelial cell activation [293]. However, no association between serum levels of this molecule and cIMT values was found [294].

4.2. Adipokines

Dessein et al. examined the independent relationship of the total and high molecular weight concentrations of adiponectin with cardiometabolic risk factors and surrogate markers of enhanced early atherogenesis in black and white patients with RA [295]. Both populations exhibited a positive adiponectin–blood pressure correlation and an inverse adiponectin–glucose concentration association [295]. However, whereas a positive adiponectin-favorable lipid profile interaction was found in black RA patients, a positive adiponectin–endothelial activation association in white RA participants was described [295]. On the other hand, in a study performed in RA patients undergoing anti-TNF-α infliximab therapy, high-grade inflammation was independently and negatively correlated with adiponectin circulating concentration whereas low adiponectin serum levels clustered with MetS features such as dyslipidemia and high plasma glucose levels [143]. Although no association between adiponectin circulating concentration and both cIMT [294] and coronary artery calcification [296] has been demonstrated, an independent relationship between total and high molecular weight adiponectin concentration and reduced plaque prevalence in RA patients with abdominal obesity or clinical absent joint damage has been described [297].

Circulating levels of leptin have been implicated in the development of CV events in RA. In this context, a positive correlation between body mass index and leptin serum levels in patients undergoing anti-TNF-α infliximab therapy was reported [154]. Moreover, a significant interaction between leptin circulating levels and homeostatic model assessment (HOMA)-IR index was described [296]. However, no association between leptin circulating levels and cIMT was found [294].

The role of leptin/adiponectin has been related to MetS risk factors and this ratio has been proposed to be an independent factor for the prediction of CV risk in RA [298].

A positive correlation of CRP and ESR with Resistin serum levels was found in patients with RA [162,299,300]. Because of that, it could be plausible to think that resistin concentrations may play a relevant role in the augmented CV risk observed in RA. In keeping with that, a relationship between Resistin circulating concentration and endothelial cell activation was described [301]. However, no association of resistin concentrations with cIMT [294] or coronary artery calcification [296] has been demonstrated.

No association between circulating visfatin concentrations and cIMT [294] and coronary artery calcification was found [296]. Similarly, circulating visfatin levels were unrelated to disease activity, adiposity, and MetS or CV mortality in RA patients undergoing anti-TNF-α therapy [302].

4.3. Biomarkers of endothelial cell activation and inflammation

Endothelial cell adhesion molecules such as intercellular adhesion molecule (ICAM)-1, ICAM-3, vascular endothelial adhesion molecule (VCAM)-1, P-selectin and E-selectin are biomarkers of endothelial activation and atherosclerosis [303]. Variations in the concentration of soluble endothelial cell adhesion molecules have been found directly associated with the development of CV disease [304,305]. Regarding RA, following a single anti-TNF-α infliximab infusion a reduction of soluble (s)ICAM-1, sICAM-3, sVCAM-1, sE-selectin, and sP-selectin levels was observed in patients with severe disease undergoing period treatment with this biologic agent [306]. However, whereas elevated soluble levels of VCAM-1 were found related to cIMT and carotid plaques [291], no association between levels of ICAM-1, ICAM-3, P-selectin, E-selectin with cIMT or carotid plaques was found [307].

Angiopoietin-2 (Angpt-2) is a pro-inflammatory marker [136] of endothelial cell activation required for the formation of blood vessels [308] that participates in the communication of endothelial cells with the surrounding mesenchyme to establish stable cellular interactions [309]. A role of this protein as a mediator of angiogenesis as well as the influence of Angpt-2 on the regulation of endothelial integrity has been postulated [310]. A study performed in recent onset RA revealed that patients with CV disease exhibited higher Angpt-2 serum levels than those without this complication [308]. A correlation between age at the time of disease onset and Angpt-2 was observed in Spanish RA patients. Angpt-2 serum levels also correlated positively with extra-articular disease. Moreover, Angpt-2 levels were higher in RA patients with CV disease than in RA patients without CV complications [311].

OPG is a protein with a pivotal role in bone remodeling that has also been implicated in the pathophysiology of RA [312,313]. This molecule has been proposed as a potential biomarker of CV risk since increased levels were associated with CV disease in non-rheumatic individuals [69]. An association between elevated OPG serum levels and both increased prevalence of carotid artery plaque [314,315] and enhanced endothelial cell activation [315] has been documented in patients with RA. Additionally, a relationship between OPG serum concentrations and the prevalence of CV events in RA has also been disclosed [316].

OPG acts as a soluble neutralizing receptor for a member of the TNF superfamily, TNF-related apoptosis-inducing ligand (TRAIL). This is a molecule that exhibits anti-inflammatory and anti-atherosclerotic properties [317–319]. TRAIL can be expressed as a trans-membrane protein or secreted as a soluble molecule [320]. Low TRAIL circulating concentration has been associated with poor outcome in patients with heart disease including those with acute myocardial infarction and heart failure [321–323]. Regarding RA, TRAIL not only participates in its pathophysiology [324] but its serum concentrations are also markedly reduced and associated with the development of heart failure [325].

Dimethylarginines are endogenous guanidine-substituted analogues of l-arginine, the precursor of NO, which are naturally liberated in biological fluids following proteolysis [326]. Among them, asymmetric dimethylarginine (ADMA) has been proposed as a biomarker for endothelial dysfunction and a CV risk factor [327,328]. Furthermore elevated ADMA serum levels have been associated with hypertension [329], hypertriglyceridemia [330], hypercholesterolemia [331], diabetes mellitus [332], IR [333] and with inflammatory diseases such as RA [334]. A correlation between elevated serum levels of ADMA and markers of active inflammation and oxidative stress has been observed in RA patients [335]. On the other hand, symmetric dimethylarginine (SDMA), the structural counterpart of ADMA, affects vascular haemostasis [336] and has been described as an independent CV risk factor in non-rheumatic individuals [337–339]. A positive relationship between SDMA serum levels and both insulin sensitivity and disease activity score was described in RA patients [326]. However, a lack of association between serum concentrations of this molecule and traditional CV disease risk factors and markers of systemic inflammation in RA was disclosed [340].

5. Current situation and future perspectives

RA has an impact on several physical and mental functions and influences activities of daily living and participation in social situations. Since

RA affects between 0.5%-1% of the adult population worldwide [1,341], this pathology leads to a considerable burden on society in terms of morbidity, long-term disability, direct (both medical and non-medical) and indirect (derived from the impact on productivity) costs [342,343]. Over the past decade, research on mortality in RA has gained momentum. These studies have consistently demonstrated an increased mortality in patients with RA when compared with expected rates in the general population [344–350]. The standardized mortality ratio in these patients varied from 1.28 to 2.98 and has remained unchanged over the past two to three decades [345]. A number of investigators have examined the underlying causes for the observed excess mortality in RA and they have demonstrated that this is largely attributable to CV disease [1–4,6,7,9,351].

Current CV risk stratification in RA is based on strategies used for the general population. In this regard, based on a pool of datasets from 12 European cohort studies, mainly carried out in general population settings, European experts performed the systematic coronary risk evaluation (SCORE) project to develop a risk scoring system to use in the clinical management of CV risk in the European clinical practice [352]. On the other hand, the Framingham Risk Score is the gender-specific algorithm more commonly used in North-America to estimate the CV risk of an individual [353].

The updated version of the SCORE and the Framingham score estimate the absolute 10-year risk for fatal CV disease events and any CV disease event, respectively [352,354]. Thresholds of a SCORE of 5% or more and a Framingham score of 20% or more are considered indications for intensified risk factor management mostly with CV drugs and particularly statins [352,353]. Regrettably, adequate stratification of the CV disease risk in patients with RA is still far from being completely established. Classic risk algorithms, mainly based on traditional CV risk factors, used to estimate the CV disease risk in the general population underestimate incident CV event rates in patients with RA [355]. More importantly, reports showing RA patients who did not reach values to be considered as having high CV disease risk according to these CV risk estimates, such as the SCORE modified according to the European League Against Rheumatism (EULAR) recommendations [356], that experienced CV complications, mainly ischemic heart disease, have been reported [20]. In addition, several studies have confirmed that many patients with RA included in the category of moderate CV risk according to CV disease risk algorithms have carotid plaques [39,40] and, therefore, should be considered as very high CV disease risk patients.

Therefore, the search for additional tools that may help to identify high-CV disease risk patients, who may benefit from active therapy to prevent CV events, is needed. It may be of major importance in RA patients that are not included in the categories of high or very high CV risk according to the classic risk assessment algorithms.

Non-invasive surrogate markers that can be used in the daily clinical practice have been found useful to identify RA at risk of CV events. Both abnormally high values of cIMT as well as the presence of carotid plaques were found as excellent predictors of future CV events in RA [22,23].

Since CV disease in RA is the result of a complex interaction between classic CV risk factors a genetic component and inflammation, the search for additional markers of CV is of major importance. As discussed throughout the review, several genetic factors exert influence with different effects on the risk of CV disease in RA [19,24,25,36,48–51,56–60,76,77,92,103,108,118,119,179,181,186,209,235,236,239,253,266–268,271]. In consequence, an important step forward may be to create a consistent set of genetic markers that would eventually be introduced into a standardized microarray and may be used as a guide for the CV disease risk stratification of patients with RA. Therefore, commercial genetic chips would be used as an additional tool to predict each RA patient's probability of developing CV disease based on the genetic background.

Variations in serum levels of several MetS-related biomarkers, adipokines and biomarkers of endothelial cell activation and inflammation appear to be implicated in the augmented CV risk observed in RA patients [143,154,162,291–293,295–301,307,308,311,314–316,325,335,336]. In this context, the information derived from the studies on biomarkers detailed in this review would be used to design a specific commercial multiplex assay. This technique would allow us to test simultaneously the serum levels of all biomarkers related to the development of CV disease offering a better CV risk characterization of each RA patient diagnosed.

In summary, current CV disease risk assessment algorithms underestimate the actual CV risk in RA. Accordingly, an adequate CV disease stratification in these patients would include the following steps

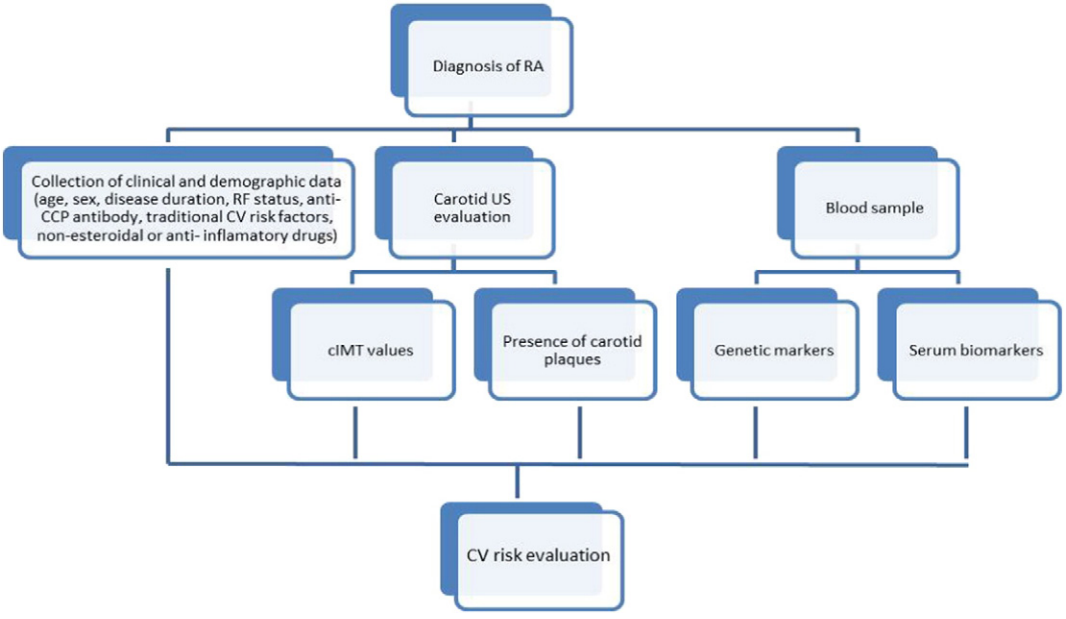

Fig. 1. Proposed CV disease risk assessment in patients with RA. To perform an adequate CV stratification in patients with RA, the following steps would be performed: 1) Collection of clinical and demographic data (age, sex, disease duration, RF status, presence/absence of anti-CCP, traditional CV disease risk factors and intake of non-steroidal or anti-inflammatory drugs). 2) A carotid US evaluation to determine cIMT values and the presence/absence of carotid plaques. 3) Blood sample collection to obtain DNA and serum. DNA would be used to identify genetic markers (by microarrays) and serum to assess biomarker circulating levels (by multiplex assays). CV: cardiovascular; RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; US: ultrasonography; cIMT: carotid intima–media thickness.

(Fig. 1): 1) Collection of clinical and demographical data (including information on age, sex, disease duration, rheumatoid factor status, presence/absence of anti-CCP, traditional CV risk factors and intake of non-steroidal or anti-inflammatory drugs); 2) A non-invasive carotid ultrasound assessment to determine cIMT values as well as the presence/absence of carotid plaques; 3) Blood sample collection to obtain both deoxyribonucleic-acid (DNA) and serum of each patient with RA. Following this procedure, DNA would be used to evaluate the genetic background of patients by genetic microarrays. On the other hand, multiplex assays would be performed on serum samples to assess the circulating levels of MetS-related biomarkers, adipokines and biomarkers of endothelial cell activation and inflammation. The combined effort of these 3 areas would lead us to a better CV disease risk stratification in RA. It would allow us to determine the best therapeutic approach for each individual patient, preventing or delaying the onset of CV events.

Take-home messages

- Current CV algorithms underestimate the actual CV risk of patients with RA.
- Carotid US is useful in the CV risk stratification of patients with RA.
- Genetic and serological biomarkers may help to identify RA patients at CV disease risk.
- Efforts focused on CV risk development calculators including new markers are underway.

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