Human Leucocyte Antigen-E

(HLA-E) in Takayasu Arteritis

Dissertation submitted to the Tamil Nadu Dr. MGR Medical University, Chennai, in partial fulfilment of the requirements for the DM Branch IX (Rheumatology) examination August 2015

Certificate

This is to certify that the dissertation entitled "Human Leucocyte Antigen-E in Takayasu Arteritis" is a bona fide work done by Dr. Ruchika Agrawal, Christian Medical College, Vellore, in partial fulfilment of The Tamil Nadu Dr. M.G.R. Medical University rules and regulations for award of DM Branch - IX (Rheumatology) under my guidance and supervision during the Academic year 2012 to 2015.

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Human Leucocyte Antigen-E (HLA-E) in Takayasu Arteritis by 161219021. Dm-rheumatology Dr Ruchika

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December 15, 2014

Ref: IRB-A1- 8.12.2014

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Ref: IRB Min No: 8156 dated 9.1.2013

Dear Dr. Ruchika Goel,

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Dr Ruchika Agrawal

Index

Title

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Introduction

Takayasu arteritis (TA) is a large vessel vasculitis characterised by inflammation in arterial walls of large arteries ultimately leading to stenosis and/or aneurysms in aorta and its main branches.

Understanding of pathogenesis and pathology in this disease is limited, even after 100 years of existence of this entity in medical literature. This is mostly due to rarity of the illness in most parts of the world and also due to paucity of available arterial tissue for research. India, however, is a large reservoir of TA. Although studies from India on TA do exist including clinical descriptions and some immunological insights, till recently there was no satisfactory disease assessment tools for TA. The later was the biggest hurdle for conducting any clinical trials in TA. Therefore, there is no standard treatment approach in TA and wide variations exist across centres in this respect. Similarly, the choice of imaging modalities, considered to be the gold standard for diagnosis of TA also vary. Our centre with a very large cohort of TA has longstanding experience and expertise in medical and interventional treatment of this disease.

Research in the field of TA, however, gained momentum in the recent years with better disease assessment tools like Indian Takayasu activity score (ITAS) and novel polymorphisms identified by genome wide association studies (GWAS) appearing in literature.

However, the many unmet needs in this area include addressing treatment outcome, damage and their predictors in the light of genetic background and immunological basis of the disease.

We have identified human leucocyte antigen class Ia as an emerging candidate gene loci for diseases like TA. HLA-E, a class Ib molecule acts as ligand for cells of both innate and adaptive immune system. It has a dual role in regulation of cytolytic activity of NK cell and cytotoxic T cells, the cells shown to be present in infilterate in rare arterial biopsy specimens of TA patients. Relevant immunogenic role of HLA E variants in relation to TA are detailed under the review of literature in the following section.

Review of literature

Takayasu arteritis (TA) is prototype large vessel vasculitis characterised by granulomatous inflammation followed by stenosis and/ or aneurysms of aorta, its main branches and pulmonary arteries (1). The untreated inflammation often leads to stenosis or occlusions of involved arteries and less frequently dilatation or aneurysms. Interestingly, Mikito Takayasu presented a patient with retinal arterio-venous anastomosis as manifestation of TA at 12th Annual Meeting of the Japan Ophthalmology Society in 1905 after 75 years of the first description of this illness by another Japanese physician in 1830. This medical condition was, however, named as Takayasu arteritis in 1975 by the Japanese Department of Health and Family welfare (2).

TA is a rare disease and more commonly affects young females especially amongst Asians (3,4). Most case series report a female predominance with reported prevalence between 82.9% and 97.0%, though female:male ratio is less skewed between 1.6:1 and 2:1 in TA populations from India, Israel and Kuwait (5–7). Even after more than 100 years of its first description by Mikito Takayasu, the pathogenesis and natural course of disease remains largely unclear. Until 1988, there was no diagnostic or classification criteria for this disease which made it difficult for researchers to perform clinical studies and multi-centric research. Ishikawa proposed first set of criteria in 1988 which included 2 major and 9 minor criteria (5). The criteria was improved in 1990 by American college of Rheumatology and till date, the ACR 1990 classification criteria (**Table 1**) is the most widely accepted for classifying TA (6).

Table 1: American College of Rheumatology 1990 classification criteria for TA (6)

Age at disease onset <40 years	Development of symptoms or findings related to TA at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of 1 or both brachial arteries
Blood pressure difference >10 mmHg	Systolic BP difference greater than 10 mmHg between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

The presence of 3 or more criteria classifies a patient as TA with a sensitivity of 90.5% and specificity of 97.8%. However, in Indian patients the sensitivity may be lower between 60.4% and 77.4% (7).

The disease presents with a wide spectrum of clinical manifestations depending on arterial territory involved and the stage of disease. Based on limitedly reports of histological studies in TA, 3 phases of the disease have been identified: i) Active phase characterised by inflammatory infiltrates of lymphocytes and macrophages with or without granuloma formation ii) Chronic phase with fibrotic lesions devoid of inflammatory cells in arterial wall and iii) an overlap of these 2 phases ie. admixture of both active and fibrotic lesions (8). The

disease in initial active pre-pulseless phase has active arterial lesions which may present as pyrexia of unknown origin along with other general systemic manifestations. Loss of arterial pulse, vascular bruits, hypertension (HTN) and other ischemic features are the predominant presentations in the chronic phase characterised by fibrotic lesions in the involved vessel. Most often, however, the histology is characterised by both active and chronic changes, thus warranting immunosuppression in all types and stages of presentations. Many patients in the fibrotic phase present with complications. Ishikawa and Maetani, in their study on prognosis of TA patients have defined complications as the presence of at least 1 of these conditions caused by TA: (1) microaneurysm formation in retina or stage 2 retinopathy; (2) severe hypertension (defined as systolic brachial blood pressure of ≥ 200 mmHg or diastolic pressure of ≥ 110 mmHg; or popliteal pressure of ≥ 230 mmHg systolic or ≥ 110 mmHg diastolic) (3) Moderate to severe (Grade 3+ or 4+) aortic regurgitation; and (4) demonstration of an aortic or arterial aneurysm with a diameter more than twice the normal on angiography (9).

Patients with 2 or more of these complications, including Takayasu retinopathy, HTN, aortic regurgitation, and aortic or arterial aneurysm were also considered to have major complications, even if each of the complications did not meet the criteria listed above.

The above mentioned authors, however, did not include optic atrophy, dilated cardiomyopathy, cerebrovascular accidents which are known complications of TA and may be the cause of mortailty in TA.

Conventional angiography is, by far, considered as the investigation of choice or gold standards for diagnosis of TA which characterises the luminal narrowing caused by unabated inflammation. Angiographically, the disease can be subdivided into 5 types according to classification proposed by Hata and Numano etal (10) (Table 2).

Table 2: Angiography classification of Takayasu arteritis (10)

Type	**Vessel involvement**
Type I	Branches from aortic arch
Type IIa	Ascending aorta, aortic arch and its branches
Type IIb	Ascending aorta, arch of aorta and its branches, descending thoracic aorta
Type III	Thoracic descending aorta, abdominal aorta, and/or renal arteries.
Type IV	Abdominal aorta and/or renal arteries
Type V	Combined features of Type IIb and IV

Involvement of coronary arteries is labelled **C (+)** and involvement of pulmonary arteries is denoted as **P (+).**

The reason for varying vascular territorial involvement is not known. Weyand etal in their work on the Toll like recptor profile of different arteries obtained from biopsy of surgical specimens had thrown light on this aspect. The authors in their study showed a similar toll like receptor profile for carotid and iliac arteries which are high expressors of TLR- 1, 3,4,5, 6 and 8 as well as shared high levels of CD11c transcripts (indicates dendritic cells) by these large artery branches. However, the subclavian, mesenteric and temporal arteries had similar

TLR expression profile which was completely different from that of carotids, iliac arteries and aorta. This differential expression of TLRs and Dendritic cells may possibly explain to an extent the inflammation restricted to certain anatomic areas within the vascular tree in TA (11). Imaging modalities like MR angiography, CT angiography, colour Doppler ultrasound and 18 FDG PET/CT has recently gained ground for early diagnosis in pre-pulseless phase (12–19). These modalities can demonstrate early inflammatory signs (vessel wall thickening and mural inflammation) as well as late complications (stenosis and aneurysms).

Till two years ago, there was paucity of prospective follow up studies in TA. One of the earliest studies by Kerr etal in 1994, reported prospective follow up data of 60 TA patients. Another Indian prospective study on treatment naïve TA patients (n=60) from SGPGIMS, Lucknow, reported azathioprine with prednisolone as efficacious in halting angiographic progression over a 1 year follow up period (20). Since then, however, all the other studies including another one from India have been retrospective in nature (21–26). While, studies from NIH cohort and Cleveland Clinics have used NIH criteria for defining disease activity (27), other studies were descriptive and have not used any objective tools for assessment of disease activity.

Disease activity assessment in TA is the most challenging task and probably the Achilles heel in management of patients with this medical condition. Currently Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most widely used laboratory parameters to define disease activity. However, in 20-40% of cases, there is a discrepancy in activity assessment by acute phase reactants like ESR or CRP values when compared with

concommittant histopathology (21,26). There are currently 2 clinical tools available for monitoring disease activity in TA. NIH criteria (27) was the first criteria proposed by Kerr et al; they defined active disease as new onset of or worsening of at least two of the following domains 1) systemic symptoms or signs i.e. fever, arthralgia, myalgia that are not attributable to other medical conditions 2) rise in ESR or CRP values without any evidence of infection /malignancy 3) signs or symptoms of vascular insufficiency, 4) lesions in originally unaffected vascular territory as detected by serial angiograms or other imaging studies. Subsequently, in order to provide a more objective criteria, Indian Rheumatology Association Vasculitis Group (IRAVAS) has devised a clinical score namely Indian Takayasu Arteritis Activity Score 2010 (ITAS-2010). This score is derived from a Disease extent score in TA (DEI.Tak), which was designed by IRAVAS to capture disease extent in TA. DEI.Tak itself has been derived from Birmingham vasculitis Index (BVAS) (28) and contains 7 main domains covering different organ systems (29). ITAS 2010 is a weighted score capturing new onset of signs and symptoms in 6 organ systems with an extra weightage given to the cardiovascular system. The authors have proposed a cut off of ITAS 2010 ≥ 2 for defining the disease as active. ITAS-2010 has been validated on Indian patients with TA. The same group has also proposed the addition of ESR and CRP scores to ITAS score and the new score is called ITAS-A.ESR and ITAS-A.CRP respectively. An arbitrary cut-off value of 5 has been proposed for ITAS-A to define active disease (30). The limitations of ITAS 2010 score is its inability to assess disease activity at the baseline visit of patient; moreover, comparison of absolute values between serial visits is difficult, as it is not an additive score. In addition, ITAS has not been designed to monitor patients who had undergone endovascular stent or

revascularisation procedures; therefore, reappearance or disappearance of arterial pulses as a result of patency status of stents cannot be interpreted appropriately in scoring disease activity by this instrument. Endovascular revascularisation procedures especially percutaneous trans-luminal angioplasty (PTA) followed by metallic stent placement have a tendency for in-stent restenosis (ISR) in 30%-50% of patients after 5-10 years following the procedure (29). It is very difficult to ascertain if the ISR is an outcome of disease activity or due to inherent complication of the procedure or the device in inflamed or uninflammed segment of stenosed arteries inducing mechanical injury and inflammation. This is even more difficult, if one particular intervened area gets repeatedly blocked with other un-intervened areas maintaining post procedure patency, more so without raised levels of inflammatory markers like ESR or CRP.

The pathogenesis of disease is not clearly known and therefore planning treatment and designing newer therapy is also difficult in TA. Previously published reports from various parts of the world have suggested a relapse rate upto 60% in-spite of adequate treatment; the 5yr survival is, however, more than 95% in most series. In some series, up to 20% of cases were reported to have a monophasic (21,26,27,31) course. Human Leucocyte Antigen (HLA) has been shown to be associated with almost all the autoimmune diseases in various studies across the world. Predicting the course of disease and identifying the monophasic subset is not possible at this moment. HLA B52 allele, a reported association of TA has been shown to predict major complications of the disease like aortic regurgitation, ischemic heart disease and pulmonary infarction in Japanese patients with TA (32). The same study on 85 patients

with TA has also shown association of HLA B39 with renal artery stenosis. Further, a multi-centric study on Turkish patients (n=330) showed increased prevalence of HLA B*52 in TA patients; this association was less pronounced in patients with limited angiographic type 1 disease and late onset disease (33). Recently, two GWAS studies have been performed in ethnically different patient populations with TA. The Japanese GWAS has indicated an association of HLA B*52:01 along with interleukin 12B (IL12B) gene polymorphisms with susceptibility to TA, with a combined relative risk of 3.45 (34). In addition, this study has also reported an association between IL12B polymorphism and serious complication such as aortic regurgitation in TA patients (34). Another GWAS study in Turkish and European-American patients has also reported association of HLA-B/MICA (rs12524487) and HLA-DQB1/HLA-DRB1(rs113452171) in TA with OR of 3.29 and 2.34 respectively (35). A very recent GWAS study published on Turkish patients and replicated on European- American TA patients has shown 3 associations conferring disease susceptibility to TA: i) polymorphism in IL6 (rs2069837) ii) RPS9/LILRB3 (rs11666543) located in leucocyte receptor complex (LRC) gene cluster on chromosome 19q13.4 and iii) rs2836878, an intergenic locus on chromosome 21q22 (36). Few other isolated studies including one on Indian subjects have (synopsised in table -3) indicated a role of HLA-B52 and few other cytokine gene polymorphisms in TA.

Table 3: Genetic studies in TA

Genes involved	**TA population studied**
IL12B, MLX, HLA-B	Japan (GWAS) (34)
IL12B, HLA-B/ MICA, HLA-DRB1/HLA-DQB1, FCGR2A/3A	Turkey/ US (GWAS) (35)
IL-6, RPS9/ LILRB3, intergenic region in chr 21q22	Turkey/ European- American (GWAS)(36)
HLA B 52/ HLA B*52:01	India, Japan , Mexico (37,38)
HLA B*51	India (37)
HLA B 39	Japan (32)
HLA B* 67	Japan (39)
HLA DPB1*09, HLA DQB1*1701	China (40)
IL12, IL2, IL6	Turkey (41)
FCGR2A/3A	Turkey/ N. America (35)
NFKBIL1	Japan (42)

Unpublished data from our centre have also shown association of IL-17 gene polymorphism (43) with susceptibility to TA (n=119 patients). We have also observed association of IL-6 polymorphism with fever as clinical manifestation of TA in the same study. Other than the

studies on HLA-B52 and cytokine gene polymorphisms, there are no further genetic studies in Indian patients with TA.

HLA-E belongs to the non-classical class I HLA molecules popularly known as MHC class Ib. It is expressed on variety of lymphoid cells like NK cells, B cells, T cells and macrophages even in resting stage (44). Its expression on normal human non lymphoid cells is however restricted to endothelial cells (ECs) (45). Unlike classical HLA class Ia molecule, HLA-E acts as a ligand for the cell surface receptors both in innate and adaptive immune responses. It acts as a major ligand for inhibitory CD94/ NKG2A and CD94/ NKG2B receptor expressed on NK cells and γδ T cells and thus regulates NK cell activity. It complexes with monomeric peptides derived from self like leader peptide sequences of self HLA-G and foreign antigens after immunisation and infection and this complex binds to NK cell receptor. The interaction of HLA-E with its receptors on NK cells leads to inhibition of T cell and NK cell mediated cytolysis. In addition, HLA-E acts as an antigen presenting molecule for αβ cytotoxic T cells and is thus implicated in anti-tumor and anti-viral responses (46,47). As with other non-classical HLA class Ib molecules, polymorphisms in HLA-E are limited. The most common polymorphism rs1264457 results in 15 alleles, of which, HLA-E*01:01 and HLA-E*01:03 are the most frequent. These two alleles have been observed to exist in nearly equal frequency (50%) in various populations including South Indians, Thais, Koreans, African Americans, Hispanics and Australians. However the frequency is shown to be unequal in North Indians (70% vs 30%) and the Japanese (32% vs 68%) (48–53). Possible ethnic differences may account for the heterogeneity in distribution of these alleles across

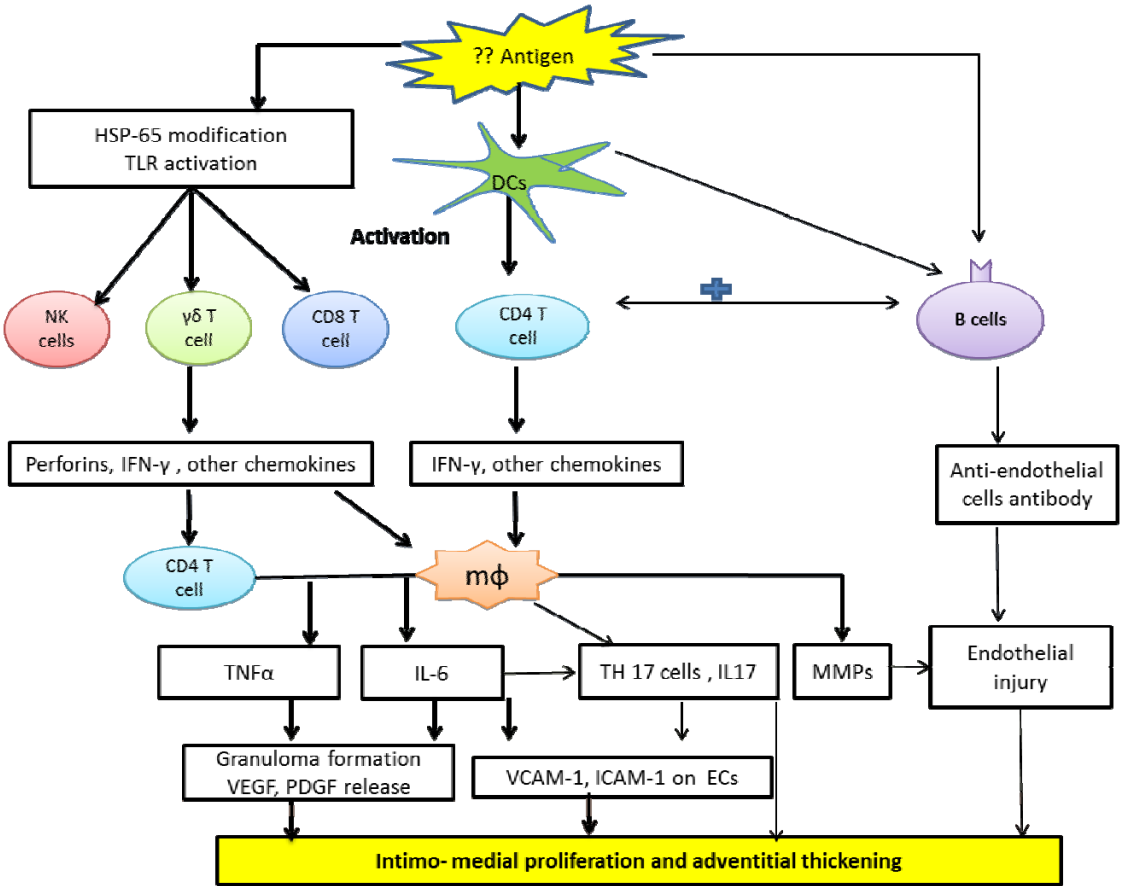
populations from different parts of India. The equal frequency of HLA-E *01:01 and HLA-E*01:03 in populations indicates a possible selection needed to maintain a balance between the two alleles. These 2 allele encode for two variants of HLA-E molecule namely ER and EG, encoded by HLA-E*01:01 and HLA-E*01:03 respectively (49,50). Structurally, the two molecules have only one amino acid difference at position 107 (arginine in HLA-E*01:01 or ER being replaced by glycine in HLA-E*01:03 or EG). In-vitro functional studies have shown differences in the two variants in terms of peptide affinity, cell surface expression, potential to inhibit NK cell lytic ability and thermal stability. HLA-E*01:01 molecule has a lower affinity to leader peptide as compared to HLA-E*01:03, which results in lower cell surface expression of HLA-E^{ER} than HLA-E^{EG}. However, the potential to inhibit NK lytic activity is more for HLA-E^{EG}(54). Further, two alleles of HLA EG i.e. HLA E*01:03:01 and HLA E*01:03:02 differ in a synonymous mutation at codon 77.

Tripathi etal in their study have shown HLA ER to be slightly more predominant than HLA EG in Indian fertile females with an allele frequency of 60% and 40% respectively (53). HLA-E*01:01 (HLA ER) has been shown to be associated with decreased risk of Behcet's disease in a study on Korean population, with HLA ER vs EG allele frequency of 40% vs 60% respectively (48). Polymorphisms in HLA-E, especially rs2844724 C/T in 3′untranslated region has been observed to be associated with occurrence of coronary artery aneuryms in Kawasaki disease and possibly this substitution may play an immunoregulatory role in expression of HLA-E on vascular endothelial cells (55). Reports of genetic association of HLA-E polymorphism with outcome of hematopoietic stem cell transplantation and age at

onset of type-1 diabetes, also endorses the role of this polymorphism in various vascular diseases. It is generally considered to be a modifier of phenotype in an existing disease rather than a susceptibility gene. Also, HLA-E*01:01 variant, which is a low expressor variant, is shown to be associated with ankylosing spondylitis, another NK cell driven autoimmune disease, in Sardinian population (56).

In spite of grey areas in the understanding of pathogenesis of TA, there are some autopsy based studies, biomarker studies and in vitro experimental studies defining the basic pathogenic mechanisms in TA as synopsized in the flow chart below. Tumor necrosis factor-α (TNF-α) and Interferon-γ (IFN-γ) are the key cytokines in initiation and propagation of granulomas in TA lesions along with contribution of various downstream cytokines like Interleukin-6 (IL-6), Interleukin-12 (IL-12), Interleukin-18 (IL-18) and possibly Interleukin-17 (IL-17). Recently TH17 cells have been shown to be increased in peripheral blood and arterial specimen of active TA patients and are shown to be resistant to the effect of glucocorticoids (57). The results of previous studies addressing the pathogenetic mechanisms in TA are summarised as below in figure 1.

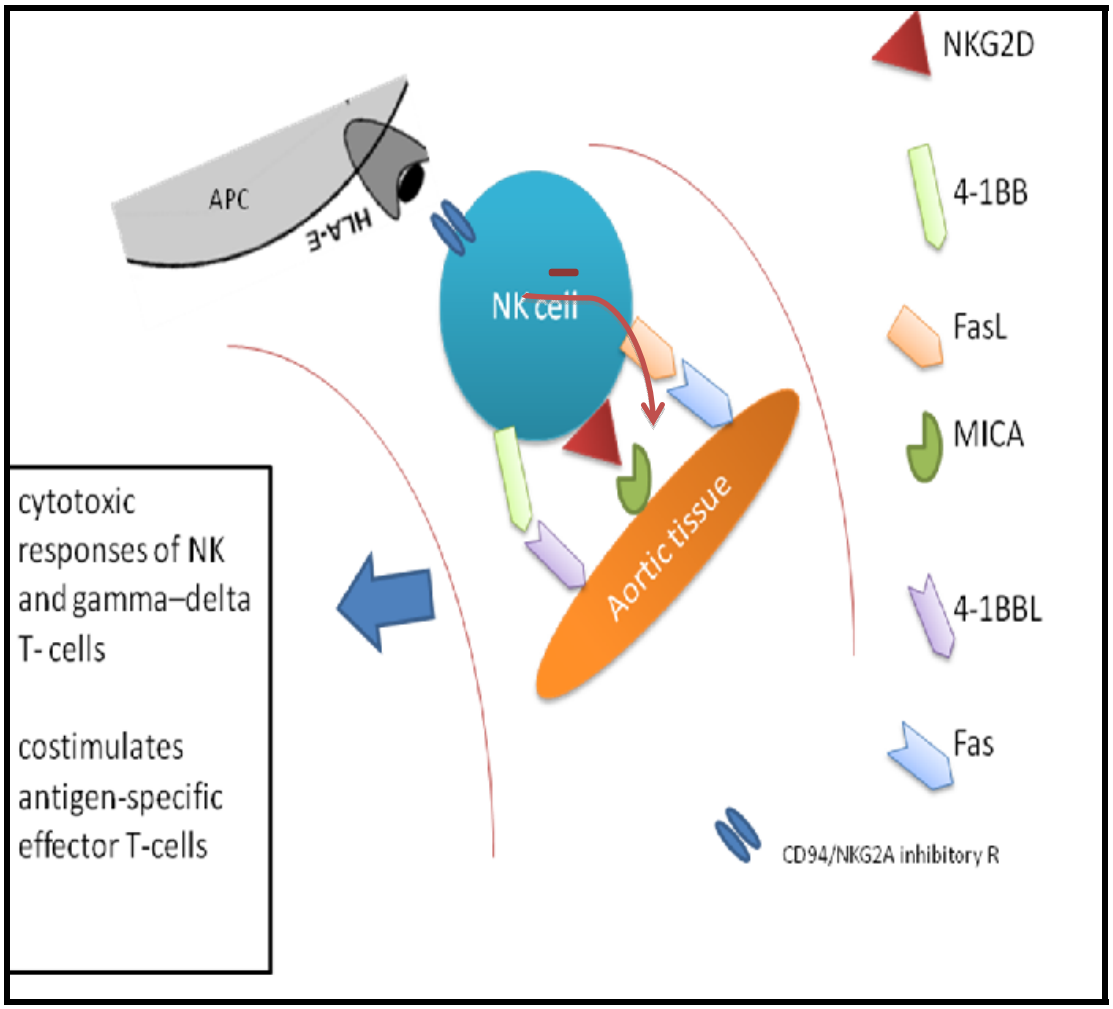
Figure 1: Proposed pathogenesis mechanisms in TA



As discussed above, cytotoxic T-cells, γδT-cells, NK cells, T-helper cells, and macrophages are observed to be the main infiltrating cells in aortic tissue of surgical specimens from large arteries of TA patients (58). Furthermore, it has been shown that aortic tissue in TA has increased expression of molecules like Fas (a death receptor on cell) and MICA, which interact with NKG2D and Fas ligand on the infiltrating NK and γδ T cells (59–61). These

evidences demonstrate the role of NK cells in mediating vascular injury in TA. Considering the importance of NK cells in pathogenesis of TA, we hypothesised that HLA-E polymorphism may have a role in pathogenesis of TA and it may have an impact on phenotypic differences among patients with TA. It may also influence the disease course and response to treatment.

Figure 2: Role of HLA-E in the pathogenesis of TA: possible mechanisms based on available data



Justification of the study

Our review of literature as detailed above, clearly explains the relevance of HLA-E in innate and adaptive immune response as well as its possible pathogenic role in several autoimmune/autoinflammatory disorders. We suspect a similar association of these variants with TA which may have some phenotypic or prognostic implications too. With this background, we decided to undertake the study in view of paucity of data on HLA-E associations in TA.

Aim and objectives

Aim: To study clinical associations of HLA-E variants (HLA-E*01:01 i.e. ER and HLA-E*01:03 i.e. EG) in Asian Indian patients with Takayasu arteritis

Objective 1: Primary objective was to study the clinical associations of HLA-E variants (HLA-E*01:01 i.e. ER and HLA-E*01:03 i.e. EG) including disease susceptibility in Asian Indian patients with Takayasu arteritis.

Objective 2: To study genotype- phenotype associations.

Objective 3: To study association of HLA-E variants with disease free survival and its predictors in our cohort of patients with TA.

Materials and Methods:

Study design: Ambi-directional case control study

This study was approved by the Research and Ethics committee of the Institutional Review Board (IRB), Christian Medical College, Vellore.

Patients and controls:

Cases: Consecutive patients with TA attending outpatient and inpatient services of Clinical Immunology & Rheumatology department (including special clinics like Lupus and vasculitis clinic, Paediatric Rheumatology Clinics) as well as Cardiology-1 clinics between 1st August 2012 and 31st December 2014 were recruited, after obtaining written informed consent.

Inclusion criteria:

1. Patients satisfying 1990 American College of Rheumatology (ACR) classification criteria for TA* as follows:
    - Age of disease onset ≤ 40 years
    - Claudication of extremities
    - Decreased Brachial artery pulse
    - Blood pressure difference of > 10mm Hg
    - Bruit over subclavian artery/ aorta
    - Arteriogram abnormality

    ****A diagnosis of TA requires 3/6 criteria to be met***

2. Those consenting to participate in the study

Exclusion criteria:

1. Patients without imaging evidence of Takayasu arteritis
2. Patients with concomitant diabetes (not induced by steroids) or any known HLA-E related genetic disease like Behcet's disease, Kawasaki disease and Ankylosing Spondylitis.

Controls: Healthy unrelated voluntary blood donors with age below 50 years.

Prospective documentation of clinical details at each visit:

New patients*- prospectively followed up: These are the patients visiting our clinics for the first time at the time of recruitment.* Details of demography including age of the patient, age at onset of disease, geographic and linguistic origin, duration of disease prior to diagnosis and co-morbidities were noted. Details of clinical presentations, complications, laboratory results, angiographic type, results of imaging studies, treatment, and toxicity of drugs were also noted. DEI.TAK was recorded for the first visit, while ITAS 2010 and TADS were prospectively calculated at each follow up visit. Though NIH score was recorded, we have not analysed that score in the present study.

Old patients *- also prospectively followed up from the time of recruitment in this study: These are our pre-existing patients attending our clinics regularly.* Details of past visits were recorded from the electronic medical records. DEI.TAK at first visit was calculated

retrospectively for these patients from already recorded clinical details. ITAS 2010 was calculated prospectively only for the visits subsequent to enrolment into the study. TADS for these patients was calculated at the last follow up visit (Proforma attached as annexure 1a, 1b, 1c).

Data was entered from clinical record form (annexure 2) into epidata software and subsequently exported to microsoft excel sheet (annexure 3) as well as SPSS version 16 for further analysis.

At each visit, the patients were classified as **active** or **stable** disease according to the following arbitrary criteria defined by us:

- **Clinical criteria of activity**

  1a. ITAS ≥ 2 (not attributable by in-stent restenosis)

  or

  1b. ITAS-A (CRP) ≥ 3, but at least one point should be contributed by clinical criteria as depicted in ITAS proforma

- **Imaging criteria of activity**

  2a. Denovo lesion on follow up angiography

  or

  2b. Stenosis of the same vessel extending beyond stent margins *

- **Laboratory criteria of activity**

Persistently raised CRP as well as ESR on 2 consecutive visits without any alternative explanation

Absence of all of these criteria was considered as stable disease

*****Isolated ISR restricted to a single stented segment alone resulting in pulse / blood pressure deficit in absence of any of the above mentioned criteria, was not considered to be a feature of disease activity. Because, ISR in multiple stented areas resulting in pulse / blood pressure deficit without any rise in acute phase reactants could be the result of intervention related injuries; and hence such scenarios were excluded from outcome analysis.

Definitions of outcome:

Complete Response: Absence of any of the above mentioned criteria defining active disease.

Partial Response: Any improvement in disease activity by the criteria adopted as above, not amounting to complete normalisation, was considered to be partial response. This includes declining or downward trend in clinical, imaging or lab criteria.

Relapse: Evidence of return of disease activity after attaining initial response as per the criteria of disease activity defined by us, at any time point during the follow up.

Treatment response: Based on these definitions, treatment response was classified as follows:

***Sustained response*:** partial or complete response sustained throughout the follow up period.

Relapsing and remitting course: Those patients responding initially, only to relapse during subsequent follow up, requiring breakthrough immunosuppression.

***Persistently active disease*:** Inability to attain partial or complete response throughout the follow up period.

Complications of TA were also noted, which were defined as presence of any of the following:

1. Accelerated hypertension or hypertensive encephalopathy

2. Moderate to severe aortic regurgitation

3. Congestive heart failure or dilated cardiomyopathy

4. Pulmonary artery hypertension

5. Cerebrovascular accident

6. Large aneurysms defined as more than 2 times increase in diameter of artery

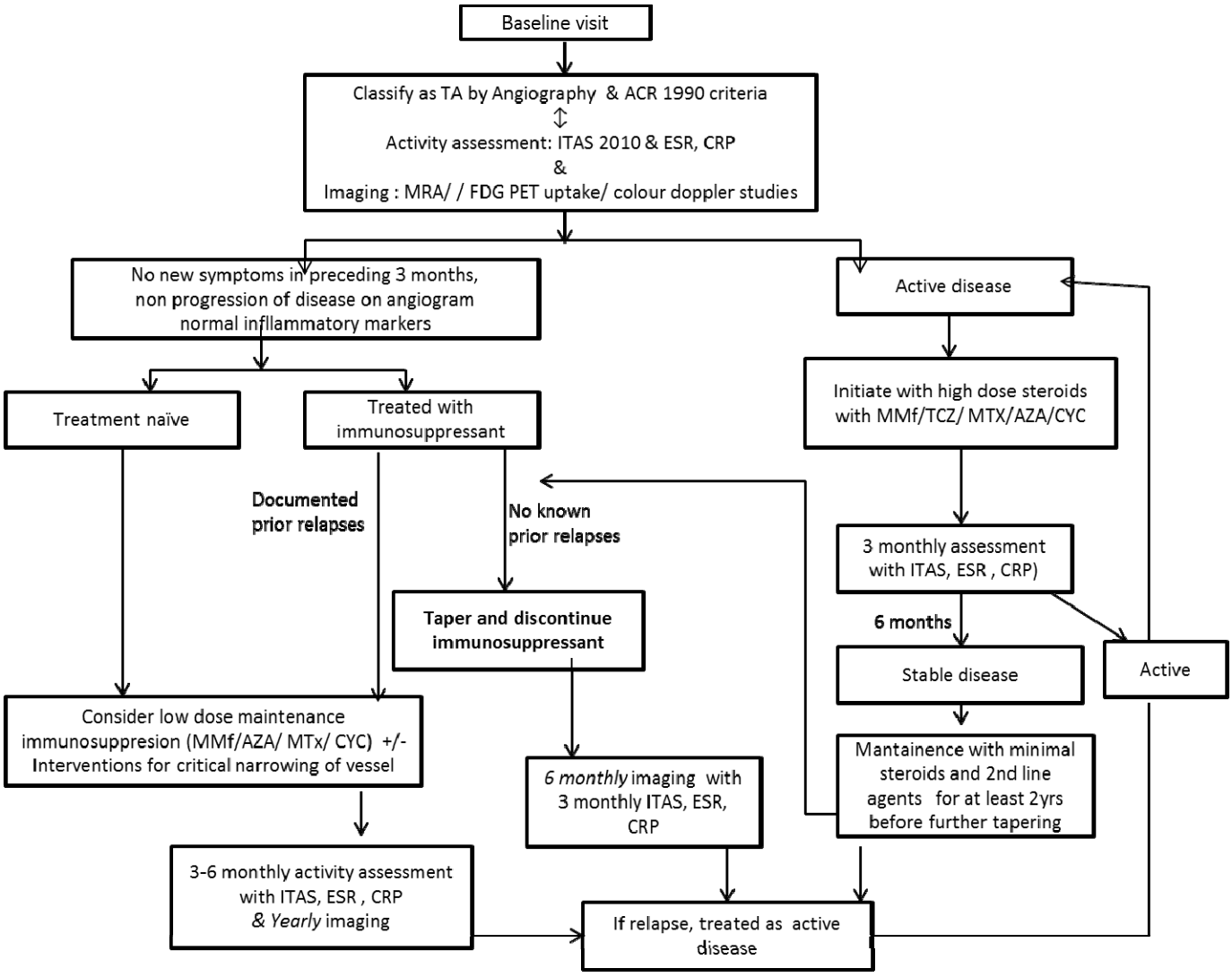
7. Chronic kidney disease or shrunken kidneys

8. Optic atrophy

9. Severe pregnancy induced hypertension with features of pre-ecclampisa

Treatment protocol: Standard treatment protocol for TA followed in our unit is shown in figure 3. In addition to medical management, endovascular interventions such as percutaneous trans-luminal angioplasty (PTA) with or without stent placement or percutaneous open balloon angioplasty were performed for symptomatic and critical arterial narrowing. In certain refractory cases i.e. in patients with uncontrolled reno-vascular hypertension, surgical procedures like renal auto-transplantation and nephrectomy were the rescue options. For large aneurysm, endovascular graft repair is the procedure of choice at our centre.

Figure 3 : Medical treatment protocol / Standard of care for TA in our unit



Genotyping methodology:

DNA extraction: DNA was extracted using GENTRA kit as per instructions below.

1. Add 3 ml of blood into a 15ml of tubes labeled with patients study no.

2. Add RBC lysis buffer and make up to 15ml. Mix by vortex or inverting 10 times and keep in ice for 15 min. Centrifuge at 4000rpm at 4°C for 10min. Discard the supernatant. White pellet formed. If the pellet is not white in colour add 3ml of RBC lysis buffer. Mix and centrifuge at 4000rpm at 4°C for 5min. Discard the supernatant.

4. Add 3ml of WBC lysis buffer. (add 4ml WBC lysis buffer if pellet is large). Incubate at 37°C for complete cell lysis. (or incubate at 55°C for 15 to 20 min). Homogenate will be formed if the cells are completely lysed. Mix vigorously.

5. Add 1ml of protein precipitate (WBC lysis: Protein precipitate = 3:1). Centrifuge at 4000 rpm at 4°C for 5min

6. Transfer the supernatant to 100% ethanol (double volume). Invert the tube slowly. DNA appears as fragments. If fragments are lesser, centrifuge at 4000rpm for 2min. Discard the supernatant and remove the settled fragments.

7. Wash DNA thrice using 1ml of 70% ethanol taken in an eppendorf tube. Take the DNA without alcohol and allow it to dry. Add 150 µl DNA hydration buffer. DNA hydration buffer should be added depending on the pellet size. Incubate at 37°C for overnight or at 55°C for 1hr for complete dissolving.

Materials required

For PCR Reaction :

Veriti 96 well thermal cycler (Applied Biosystems)

Vortex mixer , Spin win (mini-centrifuge), Micropipettes and tips,

PCR tubes (Thermo)

Mastermix (MM) (GoTaq® Colorless Master Mix for 100 reactions, Promega) stored at -20° degree Celsius which contains $MgCl_2$, dNTPs, Taq DNA polymerase at pH-8.5

HLA-E amplification primers (Sigma Aldrich): The sequence of primer was taken from molecular typing of HLA-E. The sequences were verified using Primer Blast (http://www.ncbi.nlm.nih.gov/tools/primer-blast/). The sequence of primer were as follows (54).

Name	Direction	Sequence 5′-3′	Location	Position
MSSP08079	Forward	CGAGCTGGGG CCCGACA	Exon 3	740–756
MSSP08080	Forward	CGAGCTGGGG CCCGACG	Exon 3	740–756
MSSP08088	Reverse	TTCCAGGTAGG CTCTCTGG	Exon 3	902–920

Internal control primers (located in growth hormone gene)

Name	Direction	Sequence 5′-3′
IC1	Forward	CAGTGCCTTCCCAACCATTCCCTTA
IC2	Reverse	ATCCACTCACGGATTTCTGTTGTGTTTC

Agarose gel electrophoresis:

1.5% agarose gel (Medox)- prepared by mixing 1.5gm agarose with 50ml of 0.5X Tris Borate EDTA buffer (TBE) and 50 ml of MilliQ H_2O

Ethidium bromide (10 microL)

DNA ladder (Thermo: Gene Ruler 100bp DNA ladder)

Gel loading dye (Thermo: 6X Gel Loading dye)

Electrophoresis Unit

UV transilluminator (Gel doc system- Alpha Imager HP- Cell Biosciences)

Steps in HLA-E typing by Sequence specific primer approach (SSP):

Molecular typing for HLA-E variants 01:01 and HLA-E 01:03 was performed by Amplification Refractory Mutation System (ARMS-PCR) method. The technique is based on the principle of allele-specific priming of the PCR process, i.e. a specific primer permits amplification to take place only when its 3' terminal nucleotide matches with its target sequence. The internal control primers used were located in growth hormone gene as described in materials above. This was followed by agarose gel electrophoresis using method

described by Lauterbach N etal (54). The standardization of PCR conditions was performed using DNA of healthy subjects.

The reaction mix for PCR amplification was prepared using following proportions:

Master mix	5 microL
Forward primer 1 (for HLA-E 01:01 allele)	1 microL
Forward primer 2 (for HLA-E 01:03 allele)	1 microL
Reverse primer (common for both alleles)	1 microL
Internal control (IC1)	1 microL
Internal control (IC2)	1 microL

PCR conditions were as follows

Stage 1: denaturation at 96 degree C for 2 min

Stage 2a: Denaturation at 94 degree C for 10 seconds
Stage 2b: Annealing at 65 degree C for 1 min
} X 10 cycles

Stage 3: Denaturation at 94 degree C for 10 seconds
Annealing to FP1 and FP2 at 61 degree for 50 seconds
Extension at 72 degree C for 30 seconds
} X 20 cycles

Final stage: Hold at 4 degree C

Electrophoresis time: 22 minutes

Product size: 190 bp for HLA-E alleles and 429 bp for Internal control

Interpretation:

The length of HLA-E*01:01 and HLA-E*01:03 specific fragments is 190 bp while Internal fragments are 429 bp size. If a specific fragment (190 bp) was visible for only HLA-E*01:01 and not for HLA-E*01:03, the sample was typed as homozygous for HLA-E*01:01. If the 190bp band was visible for both HLA-E*01:01 and HLA-E*01:03 fragments, it was typed as heterozygous. If only HLAE*01:03 specific fragment band was visible the sample was typed as HLA-E* 01:03 homozygous. The gel picture was captured by gel doc system from biorad.

Statistical analysis:

Software used: The data was analysed using SPSS version 16.

Cluster analysis was done using R software. Graphs were created using Microsoft excel.

Non parametric data is depicted as median with 25%-75% interquartile range (IQR).
Parametric data is depicted as mean ± S.D.

Allele frequency and genotype distribution: between cases and controls and various phenotypic disease subsets were compared using **chi-square test or Fischer's exact test**, where ever applicable. **Mantel- Hanzel correction** was applied for calculating odds ratio adjusted for sex of cases and controls. Parametric continuous variables were compared using **student t- test**. Non- parametric tests i.e. **Mann Witney U test** was used for comparison of nonparametric data like age, duration of symptoms etc. **Hochberg correction** was applied for multiple comparisons related to genotype.

The association of disease outcome with various parameters including age at onset, sex, duration of symptoms, angiographic disease type, genotype, medications, follow up duration, CRP & ESR at presentation was estimated using **univariate analysis**. Only variables with p < 0.2 were included in **multivariate logistic regression** to assess their independent contributions to outcome.

Kaplan Meier survival function was used to assess disease free survival and median survival time. 1-survival plots were constructed to depict cumulative incidence of response and relapse.

Agglomerative hierarchical cluster analysis was used to find the patterns of arterial involvement in Takayasu disease. Each arterial area was considered as one variable. Each variable were classified as either presence or absence of the lesions in various arteries. Initially, each variable or observation is regarded as a cluster in itself. Hence to start with, there were as many clusters as the number of variables. **The Euclidian distance** which is the distance between 2 clusters was computed and correlation coefficient was calculated as a measure of distances or similarities between the categorical variables. The nearest clusters were then merged together according to the measure of similarity to form a larger cluster. The iteration was repeated until all the variables were merged as a single cluster. In this analysis, we used the complete linkage method to merge two new nearest clusters.

Results

A total of 150 patients who satisfied the inclusion criteria were recruited. Also, 264 healthy unrelated blood bank donors (150 males and 101 females) were recruited as healthy controls after obtaining written informed consent.

Among 150 patients enrolled, 110 were enrolled at their 1st visit to our institution (new patients) and the remaining 40 patients were those who were already under regular follow up in our clinics (old patients). Most of the patients (n=76, 50.7%) recruited were from southern India. The table-4 below shows the distribution of geographic and linguistic origins of the whole cohort (patients and controls).

Table 4: Geographic origin of Asian Indian patients with TA

Geographic location	Patients N (%)	Controls N (%)
South India (Tamil Nadu, Kerala, Karnataka and Andhra Pradesh)	76 (50.7)	219 (83)
North India (Delhi, Rajasthan, Gujarat, Bihar, Jharkhand,	29 (19.3)	19 (7.2)
Chhattisgarh)	31 (20.7)	16 (6.1)
Eastern India (West Bengal, Orissa)	14 (9.3)	10 (3.8)
North East India (Assam, Meghalaya, Tripura, Sikkim, Mizoram)		

Baseline data: The median age of patients at presentation was 28.5 (IQR 22-36.3) years with the youngest patient being 11 year old. The median age at disease onset was 24 (IQR 18-31) years. Our cohort also included a fair number of patients with childhood onset TA. Thirty five patients had disease onset before their 18th birthday; in fact, 33 out of these 35 patients

had onset of disease related symptoms before the age of 16 years. The median duration of symptoms prior to the 1st visit to our institute was 33.5 (IQR 12-72) months. The median delay in diagnosis i.e. the time duration between onset of symptoms and diagnosis of TA, was 12 (IQR 6-36) months, maximum being 180 months. Majority of our patients (n= 113, 75.3%) were females. The TADS at baseline was calculated only for 'new patients' who had documentation of all the relevant clinical data prior to coming to our institution (n=108). Baseline median TADS at the time of recruitment was 6 (IQR 3-10) with maximum score of 17.

The details of demography and disease extent at baseline visit are shown in **table 5** below:

Table 5: Baseline demography and disease extent in patients with TA

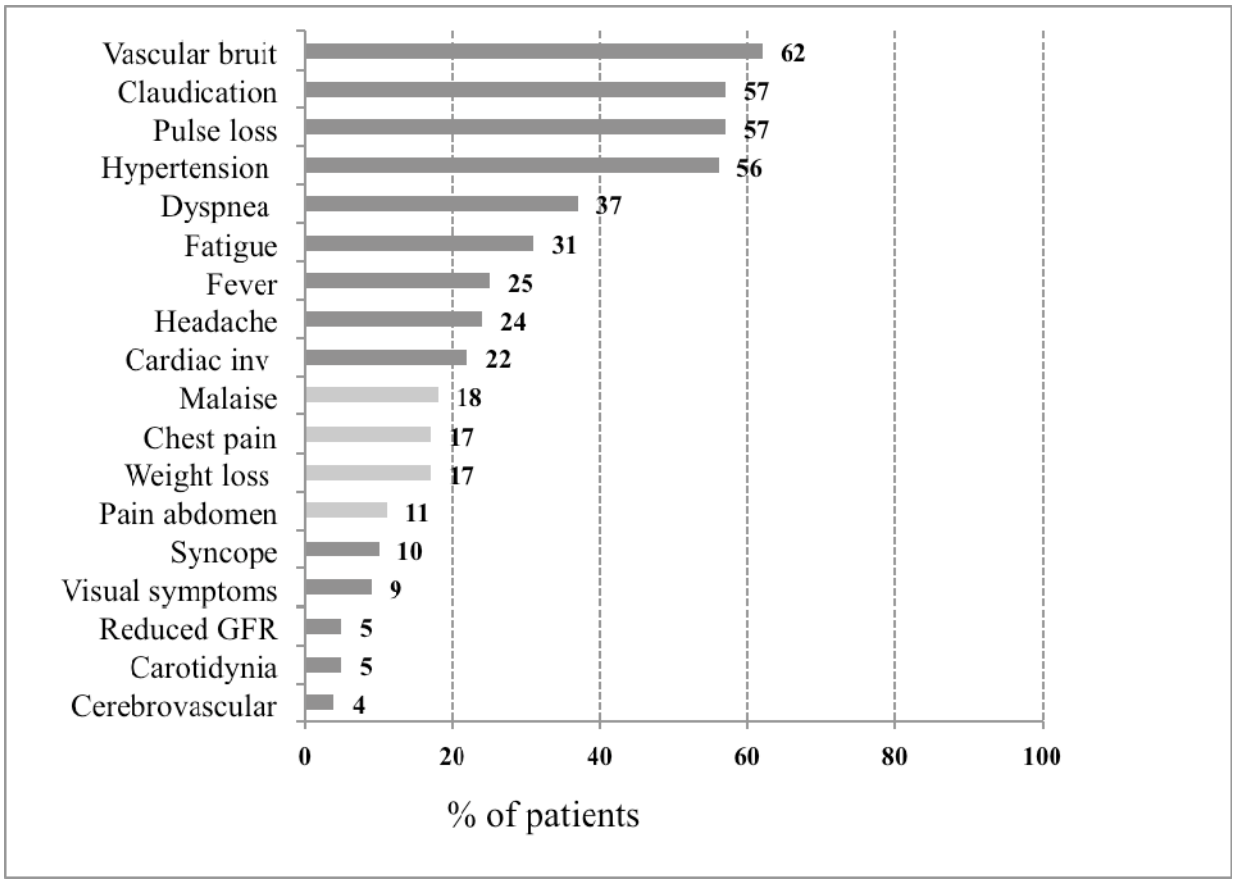
Parameter	Total patients = 150
Median age in years (IQR)	28.5 (22- 36.3)
Median age at onset in months (IQR)	24 (18-31)
Male : female	37: 113
Duration of symptoms in months (IQR)	33.5 (12-72)
Baseline DEITAK (IQR)	9 (6-13) , range 0- 27
Baseline TADS (IQR)	6 (3-10), range 0-17

Most of the patients had presented with clinical signs and symptoms pertaining to peripheral ischemia. The most common clinical presentation was presence of vascular bruit in 62% of patients, followed by pulse loss and limb claudication in 57% each, systemic hypertension

was present in 56% of patients. Systemic features were present as follows: fatigue (31%), fever (25%), malaise (18%) and weight loss (17%).

The frequencies of clinical features are shown in figure 4.

Figure 4: **Clinical features at presentation in TA**



Ninety one (60%) patients had presented with CRP values of ≥ 6 mg/L and 108 (64%) had raised ESR of > 20 mm/1st hr. Both the inflammatory markers were raised in 80 (53%) patients.

Imaging data: The complete topography of lesions could be ascertained by conventional, MR or CT angiography in 144 out of 150 patients (figure 2), while 6 patients had evidence of large arterial stenosis by regional arterial doppler imaging. Regional doppler of the affected vascular territories causing the related symptoms and signs were performed for these 6 patients. Complete vascular occlusions were seen in 95 patients (63.3%), while aneurysms in addition to vascular stenosis or occlusions were seen in 22 patients (14.7%). Among those with aneurysms, 1 patient with large aneurysm involving descending thoracic aorta (DTA) and another one with large aneurysm in brachiocephalic artery with compressive features deserve to be mentioned. Large aneurysm was defined as dilatation of more than 2 times the normal diameter at the involved segment of the vessel as mentioned under the methods section.

Type 5 disease was the most frequent subtype observed in 83 out of 144 (57%) patients. Coronary angiography was performed in 111 patients and 30 (27%) patients showed coronary artery involvement. Ninety-nine patients had also undergone pulmonary angiogram and 15 (15.1%) of them showed pulmonary arterial involvement. Left subclavian artery was the most commonly involved artery as noted in 62% of patients, followed by right subclavian artery (46%), abdominal aorta (44%) and left renal artery (43.3%) involvement. The frequency of other arterial lesions is shown in figure 5. Pure infra-diaphragmatic involvement without C+ or P+ disease (Type 4 C-P-) was seen in 22 (15.3%) patients.

Figure 5: Frequency of angiographic subtypes of TA

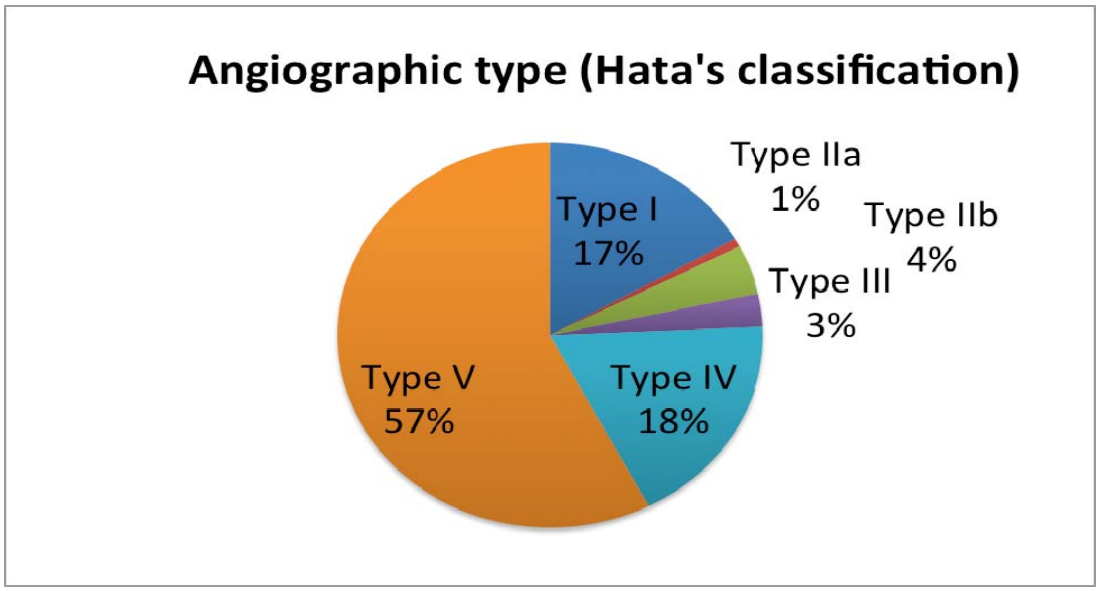
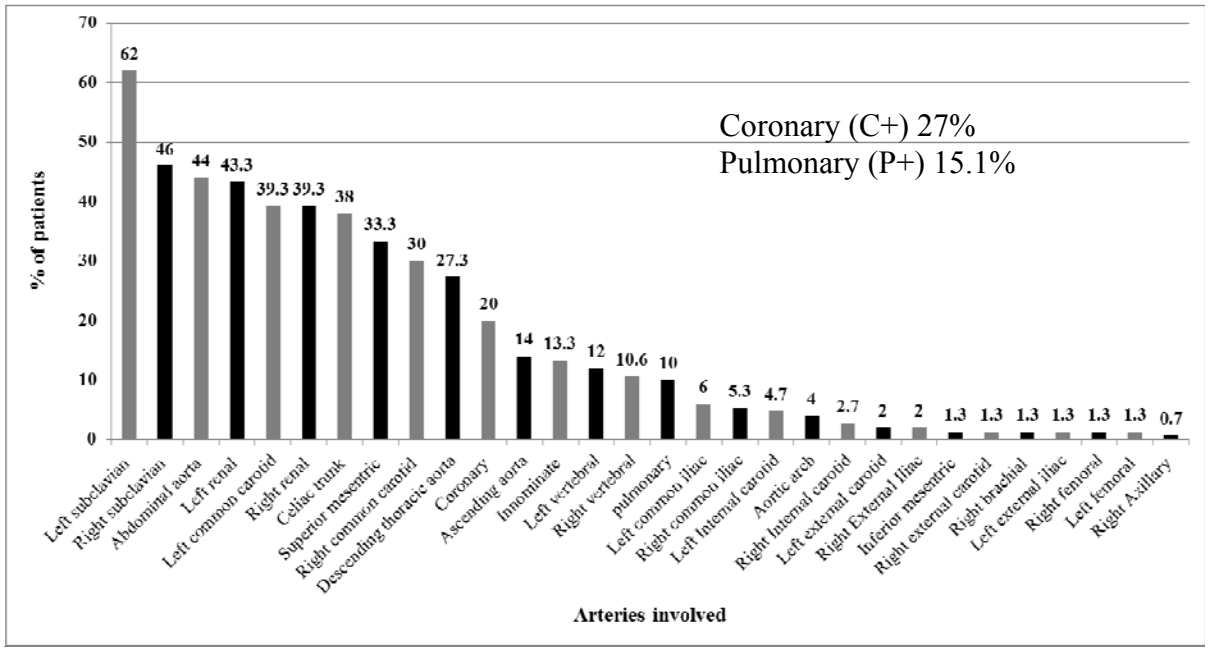


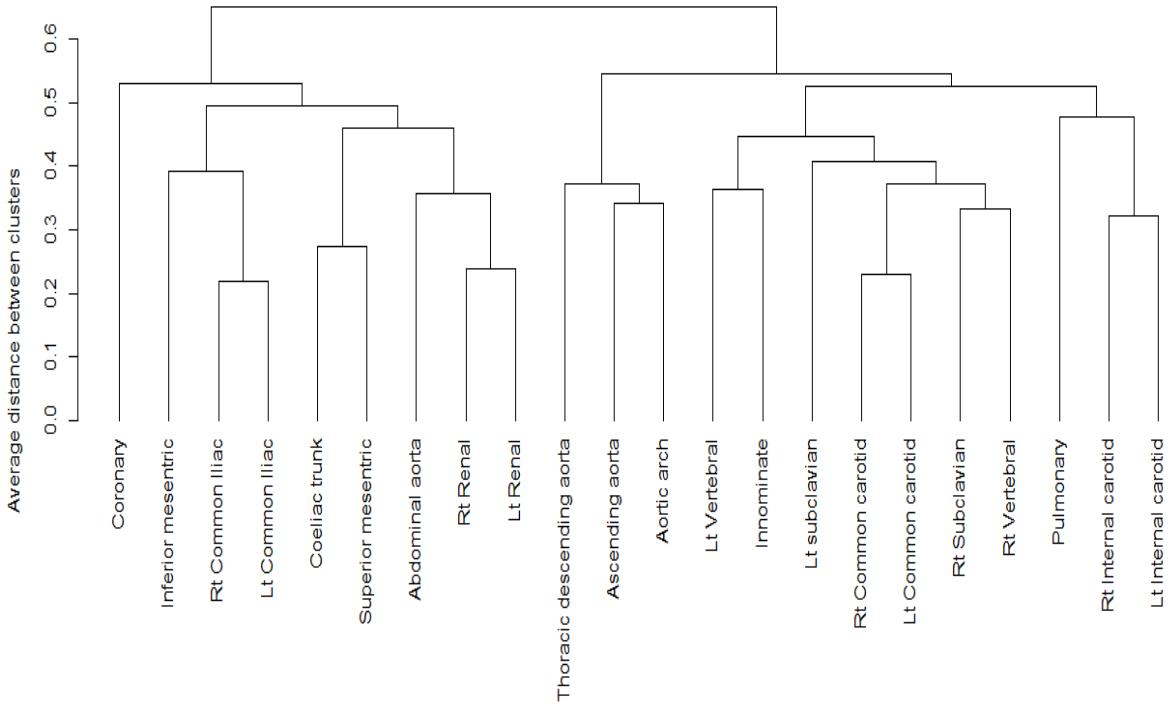
Figure 6: Frequencies of arterial involvement by imaging in 150 patients with TA*



* Angiography – 144 patients; Arterial Doppler – 6 patients

Cluster analysis: Our next aim was to analyse the pattern of vascular involvement in our patients by cluster analysis. Correlation of each pair of the 23 specific arteriographic lesions was performed using a 2x2 correlation matrix. Results of the correlation coefficient matrix are given in the data file Annexure 4). Involvement of internal iliac, common carotid and renal artery strongly correlated with their respective contralateral arterial involvement with a correlation coefficient > 0.5, thereby implying symmetrical involvement of these vessels in our patients. The next highest correlation was observed between superior mesenteric and coeliac arteries. We also observed a correlation between left and right internal carotid arteries. Right common carotid and right subclavian clustered with right vertebral artery, while a correlation was observed between aortic arch and ascending aorta and between right renal & abdominal aorta. These results imply contiguous involvement of these vascular territories in TA. Tree dendrogram (Figure 7) showed branching of the graph into 2 separate clusters at a distance of 0.55. Considering a cut off point at a distance of 0.55, we observed 2 major clusters of arterial involvement in TA viz cluster 1: consisting of coronary, abdominal aorta along with its branches (Inferior mesenteric artery, right and left common iliac arteries, coeliac trunk, superior mesenteric and right and left renal arteries) and cluster 2: consisting of rest of the other involved arteries. In summary, results of the cluster analysis suggest symmetry and contiguousness of involved vessels, as well as clustering of coronary artery involvement with pure infra-diaphragmatic large arterial disease in our patients with TA.

Figure 7: Tree Dendrogram depicting clustering of involved arteries in TA



Complications: Among the patients recruited, 53 had presented with complications as defined by us in methods. Dilated cardiomyopathy (DCMY) and moderate to severe aortic regurgitation (AR) were the most frequently observed complications (Table 6).

Table 6: Frequency of complications in patients with TA

Accelerated Hypertension /hypertensive encephalopathy	7
Moderate / severe AR	14
Congestive heart failure/ DCMY	21
Pulmonary Hypertension	3
Cerebrovascular accident	8
Large aneurysm	2
CKD/ Shrunken kidneys	6
Optic atrophy	1
Severe pregnancy induced hypertension	1

Medical treatment details: Of the 110 patients recruited at their first visit (termed as 'new patients'), 40 were already being treated with immunosuppressants including steroids prior to coming to our hospital.

Majority of the new patients (n=104) received steroid as a component of their induction regime. Nine of them received tociliumab as initial induction agent alongwith steroids ± MMf, while 2 other patients received high dose pulse steroid infusion. High dose pulse steroid was given to one patient of TA with unstable angina who subsequently developed new onset CVA during the initial visit in our hospital. Yet another patient received pulse steroid in

view of DCMY with very high inflammatory markers. Among the patients continuing on prior oral steroids, 12 of them were given low dose steroids (≤10mg/day), while the rest were on > 10mg/day dosage.

All but 1 amongst the old patients (n=39) were on oral steroids at the time of recruitment, with or without 2nd line immunosuppressants as mentioned below; 33 (%) of them were on > 10mg/day of steroids. One patient, belonging to this subset too, recieved additional tocilizumab infusion as induction agent along with steroids, in view of high disease activity at recruitment.

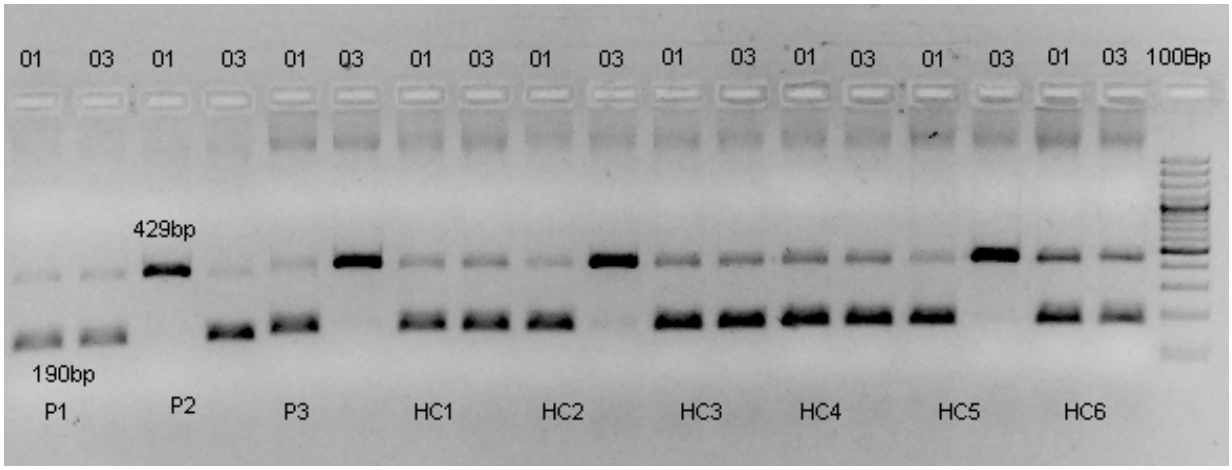
Most of the patients (n=146) were initiated on 2nd line immunosuppressants at baseline. MMf was the 2nd line immunosuppressant in most of them (n=116) followed by azathioprine (n=15) and methotrexate (n=14) in that order. Four patients were not treated with immunosuppressants, as they failed to come for follow up with the basic investigations required before starting these agents. Therefore these patients only had some baseline data and were excluded from any follow up evaluation. All patients received antiplatelet agent i.e aspirin or clopidogrel either as single agent or as combination following endovascular interventions. Anti-hypertensives and statins were added for patients with hypertension and dyslipidemia respectively.

Interventions: In addition to medical therapy, 101 patients underwent interventional procedure. Percutaneous trans-luminal angioplasty (PTA) with stenting was the most common procedure performed in 99 patients, while 2 patients underwent percutaneous open balloon angioplasty (POBA) without stent insertion. Surgical procedures performed included

coronary artery bypass graft in 2 patients (done prior to their 1st visit to us), nephrectomy, renal auto-transplantation and aortic aneurysm graft repair in 1 patient each.

Results of genotyping: The representative gel capture picture of PCR-SSP reaction for 10 patients is shown in figure 8.

Figure 8: Showing representative gel capture picture of PCR-SSP reaction for 10 patients



01 denotes HLA-E*01:01 allele

03 denotes HLA-E*01:03 allele

Amplified fragment length is 190 base pairs

Internal control: Amplified fragment length is 429 base pairs size

P1 to P3 denotes patient no. 1,2 and 3 respectively

HC1 to HC6 denotes healthy controls 1, 2 , 3, 4, 5 and 6 respectively

HLA-E genotypes in our subjects were conformed to Hardy- Weinberg equilibrium. Genotyping revealed no difference in frequency of HLA-E*01:01 and HLA-E*01:03 alleles between TA patients and healthy controls (Table 7). The frequency of HLA-E*01:01 and HLA-E*01:03 in TA patients were 51.3% (154/300) and 48.7% respectively, whereas these figures for the controls were 48.9% and 51.1% respectively. Distribution of genotypes of two alleles did not differ between patients and controls, even after adjusting for sex of the patients (adjusted OR: 0.97; 95% CI: 0.84 - 1.135; p=0.76). Subgroup analysis of patients and controls according to the geographic and lingustic distribution also showed similar results.

Table 7: Comparison of HLA-E allele and genotype distribution among cases and controls

HLA-E (rs 1264457)	Patients (n=150)	Controls (n=264)	p
Allele frequency % (n)			
*01:01	51.3% (154)	48.9% (258)	0.49
*01:03	48.7% (146)	51.1% (270)	
Genotype frequency % (n)			
*01:01/ *01:01	28.9% (43)	24.2% (64)	0.58
*01:01/ *01:03	45.3% (68)	49.6% (131)	
*01:03/ *01:03	26% (39)	26.5% (70)	

Associations of genotypes (Table 8 A & B): Our next objective was to analyse the influence of HLA-E variants on baseline phenotype of the disease. We determined the association of these alleles and genotypes with age of disease onset, angiographic subtype of disease, coronary or pulmonary involvement, systemic symptoms like fever and DCMY as complications. There was no difference observed in the frequency of the 2 alleles in relation to any of the parameters mentioned above. However, the frequency of HLA-E*01:01 homozygous genotype was significantly lower in those with pure infra-diaphragmatic (type 4 C-P-) disease, as compared to other angiographic subsets (p = 0.038). Similarly, frequency of HLA-E*01:01 homozygous genotype was significantly lower in those with DCMY, as compared to those without DCMY (p= 0.039). There was also a trend towards lower occurrence of HLA-E 01:01 homozygous genotype in those with presence of P+ disease (p= 0.06). Logistic regression was performed to assess the independent association of genotype with the relevant parameters found to be significant in univariate analysis, after adjustment for sex of the patients. This multivariate analysis revealed HLA-E*01:01 homozygous genotype to have a significant protective effect on pulmonary artery involvement (Adjusted OR 0.12, 95% CI- 0.14- 0.98, p= 0.047) and DCMY (Adjusted OR 0.2, 95% CI- 0.05- 1.03, p= 0.055) independent of any other factor. There was, however, no independent association of this genotype with type 4c-p-disease (p= 0.069), unlike the finding in univariate analysis.

Table 8A: Association of HLAE allele and genotype distribution with various clinical parameters

HLA-E (*rs 1264457*)			p
Age at onset	**<16 years (n=26)**	**≥16 years (n=124)**	
Allele			
*01:01	42.3%	53.2%	0.15
*01:03	57.7%	46.8%	
Genotype			
*01:01/ *01:01	15.4% (4)	31.5% (34)	0.1
*01:01/ *01:03	53.8% (14)	43.5% (54)	NS
*01:03/ *01:03	30.8% (8)	25% (31)	NS
Dilated cardiomyopathy	**Present (n= 21)**	**Absent (n=129)**	
Allele			
*01:01	38.1%	53.5%	**0.064**
*01:03	61.9%	46.5%	
Genotype			
*01:01/ *01:01	9.5% (2)	31.8% (41)	**0.039**
*01:01/ *01:03	57% (12)	43.4% (56)	
*01:03/ *01:03	33.3% (7)	24.8% (32)	
Fever at presentation	**Present (n=37)**	**Absent (113)**	
Allele			
*01:01	59.4%	48.7%	0.11
*01:03	40.6%	51.3%	
Genotype			
*01:01/ *01:01	37.8% (14)	25.7% (29)	0.155
*01:01/ *01:03	43.2% (16)	39.7% (52)	
*01:03/ *01:03	18.9% (7)	28.3% (32)	

Table 8B: Association of HLAE allele and genotype distribution with angiographic features

HLA-E (*rs 1264457*)			p
Angiography type (n=143)	**Type 4 C-P- (n=22)**	**Others (n=122)**	
Allele			
*01:01	43.5%	52%	0.29
*01:03	56.5%	47.9%	
Genotype			
*01:01/ *01:01	9% (2)	31.1% (38)	**0.038**
*01:01/ *01:03	68.1% (15)	41.8% (51)	NS
*01:03/ *01:03	22.7% (5)	27.1% (33)	NS
Coronary Involvement #	Present (n=30)	Absent (n= 81)	
Allele			
*01:01	58.4%	47.7%	NS
*01:03	41.6%	52.3%	
Genotype			
*01:01/ *01:01	40% (12)	22.2% (18)	**0.06**
*01:01/ *01:03	36.7% (11)	51.9% (42)	NS
*01:03/ *01:03	23.3% (7)	25.9% (21)	NS
Pulmonary Involvement #	Present (15)	Absent (84)	
Allele			
*01:01	40.5%	51.7%	0.23
*01:03	59.5%	48.2%	
Genotype			
*01:01/ *01:01	6.7% (1)	29.7% (25)	**0.06**
*01:01/ *01:03	67.7% (10)	44% (37)	NS
*01:03/ *01:03	26.7% (4)	26.2% (22)	NS

 # Coronary and pulmonary angiogram were performed in 111 and 99 patients respectively

Disease course and outcome during follow up visits (figure 9 and 14):

Altogether, 102 patients were followed up for ≥ 6 months with a median follow up duration of 17 (IQR- 10-35) months, (Range: 6-168 months). Of them, 98 patients had unambigous follow up data and hence we analysed the outcome of these 98 patients only. The follow up duration was 12 (IQR- 9-18) months for new patients (33 of them had ≥ 12 months follow up) and it was 48 (IQR- 25 to 72) months for old patients. Overall, 79 (80.6%) patients attained stable disease in response to initial treatment; and 59 patients (60.2%) sustained the response till the last follow up visit. Among the sustained responders, 52 (53%) had sustained complete response, while 7 had sustained partial response to treatment. Remaining 20 patients (20.4%) had relapsing and remitting course of disease. The median steroid dose was equivalent to 7.5 mg/day (IQR: 5-10 mg/day) prednisolone (ie. 9 mg of Deflazacort with IQR: 6-12 mg/day) at the time of relapse. Of these 20 patients, 16 had clinical and laboratory evidence of relapse, while 4 patients had only angiographic evidence of progression of disease. Five of the relapsed patients, however, responded to breakthrough escalation in treatment. These 5 patients were, however, considered to have relapsing-remitting disease.

Nineteen (19.4%) patients, however, continued to have persistently active disease throughout the follow up period in-spite of our standard treatment protocol. Of these 19 patients, 4 of them had clinically quiescent disease with normal CRP, but they had angiographic evidence of progressive disease as defined by us.

Patients excluded from outcome analysis: Disease activity assessment could not be assessed in 4 patients for reasons explained earlier. One of these 4 patients was initiated on

breakthrough tocilizumab infusion to maintain stent patency in symptomatic, critical stenosis of a coronary artery branch; this patient had repeated ISR in the stented segment alone without any other evidence of disease activity. Another patient among these was given tocilizumab due to repeated subclavian artery ISR restricted to the stented segment only. Two other patients had ITAS of >5, in whom this score was solely contributed by the weakening of clinical pulse as a consequence of ISR in the previously stented subclavian arteries without any involvement of areas beyond the stented segments. These patients had normal ESR and CRP. As we cannot rule out procedure or device related injury like barotrauma, inflammation or thrombosis itself resulting in angiographic or pulse abnormalities in these 4 patients, we have excluded them from outcome analysis.

Figure 9: Disease course in patients with follow up duration ≥ 6 months (All patients, n= 98)

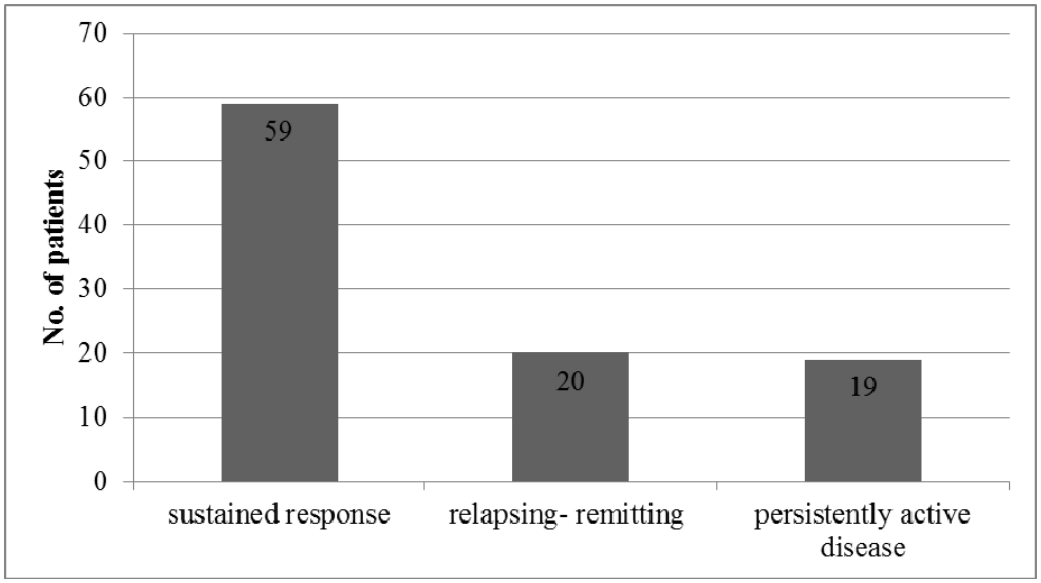
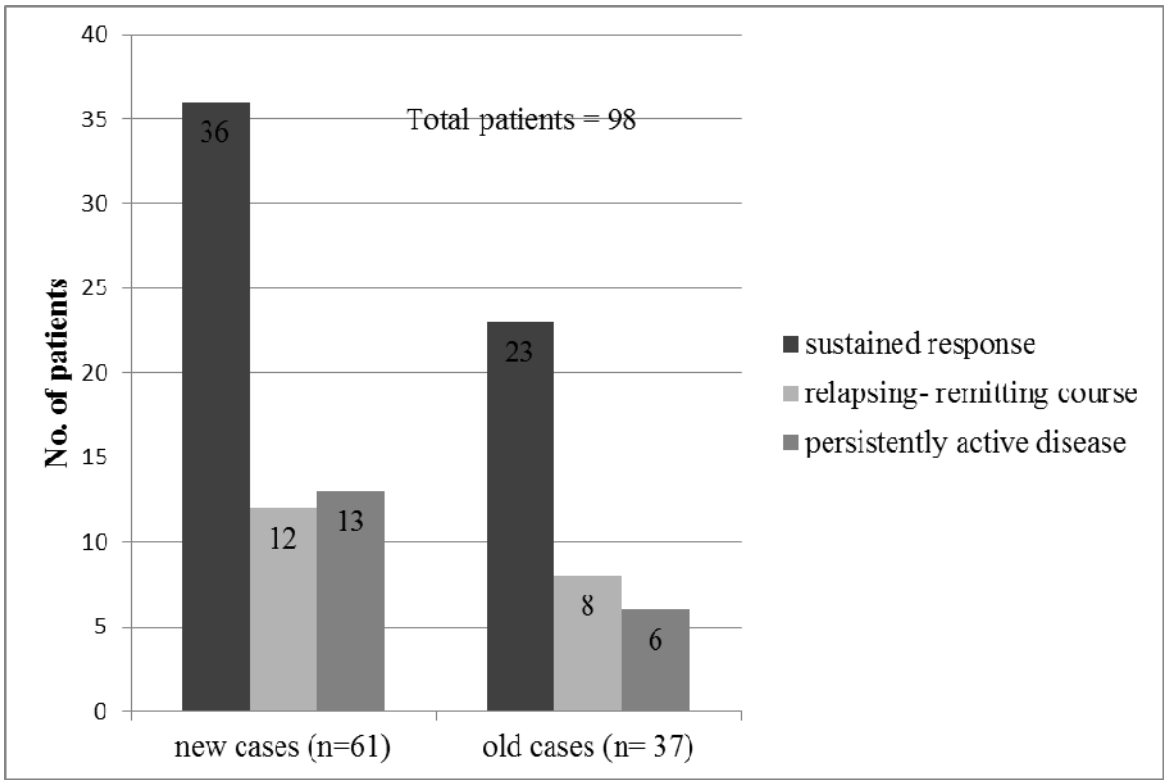


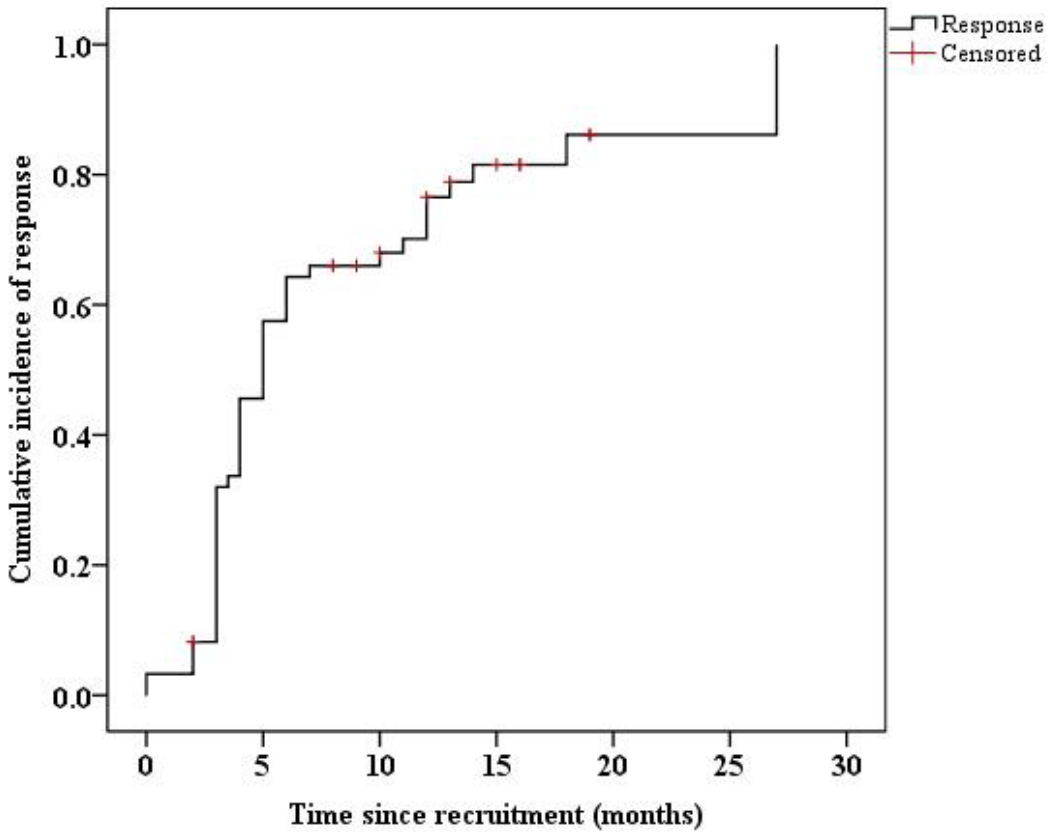
Figure 10: Disease course in patients with follow up duration ≥ 6 months (new and old patients shown separately)



New patients: Among new patients, 61 patients were followed up with us for at least 6 months. The median follow up duration for these patients was 12 (IQR 9-18, range: 6-27) months. Of these, 48 (78.7%) attained remission at a median follow up period of 5 (95% CI 4.2- 5.8) months (shown as in figure 11), while 13 (21.3%) had persistently active disease. Time to remission could not be calculated with certainty for one patient as this patient was lost to follow up for a period of >1 year only to resurface later. Among these 48 patients in remission, 12 of them had relapsed. The estimated mean time to relapse (calculated from baseline visit) in this group was 21 (95% CI: 19-24) months. Mean steroid dose initiated for

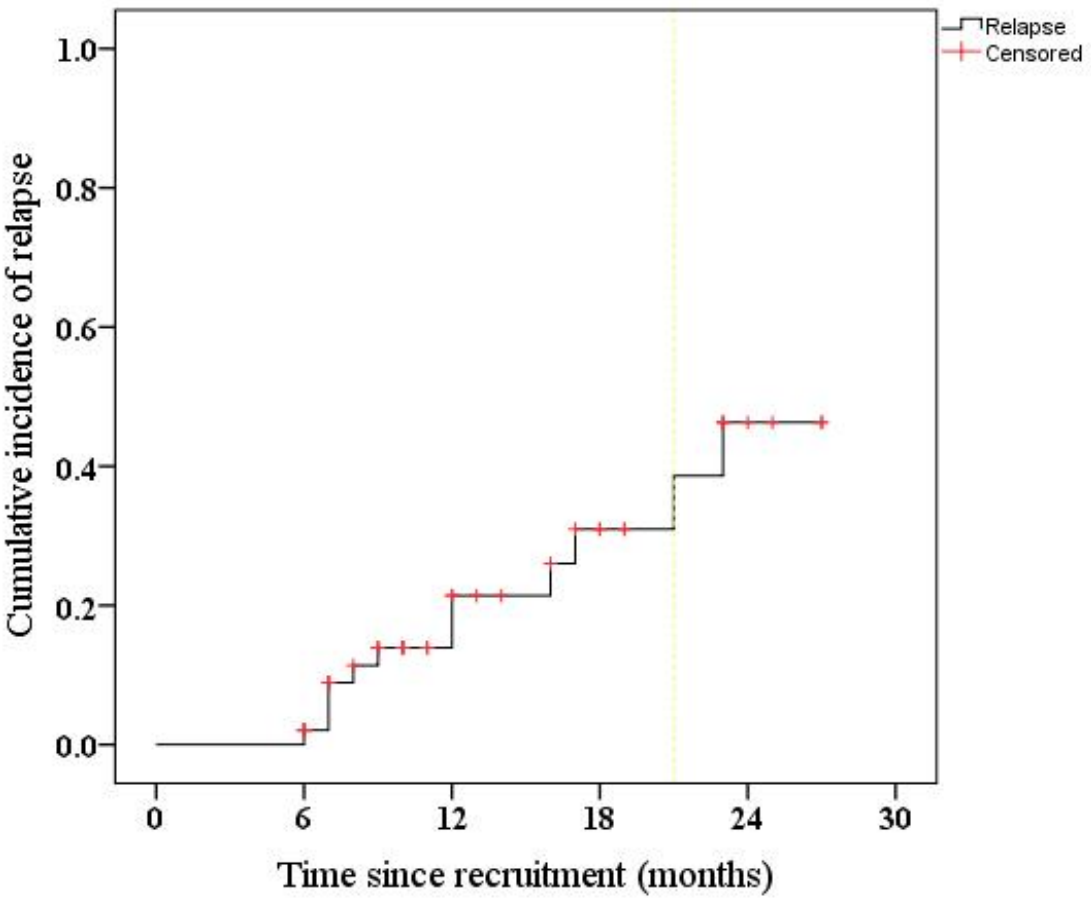
this group was equivalent to 29.5 ± 13.5 mg/day of prednisolone. The cumulative relapse rate for new patients was 20.5% at 1 year and is predicted to be 46% at 2 years as per Kaplan Meier (KM) survival statistics.

Figure 11: Cumulative incidence of response in 'New patients' with TA*



*Follow up duration of ≥ 6 months (n= 60). Time to response was recorded as 0 for the 2 patients with stable disease at recruitment due to prior treatment from another centre.

Figure 12: Cumulative incidence of relapse in 'New patients' with TA*

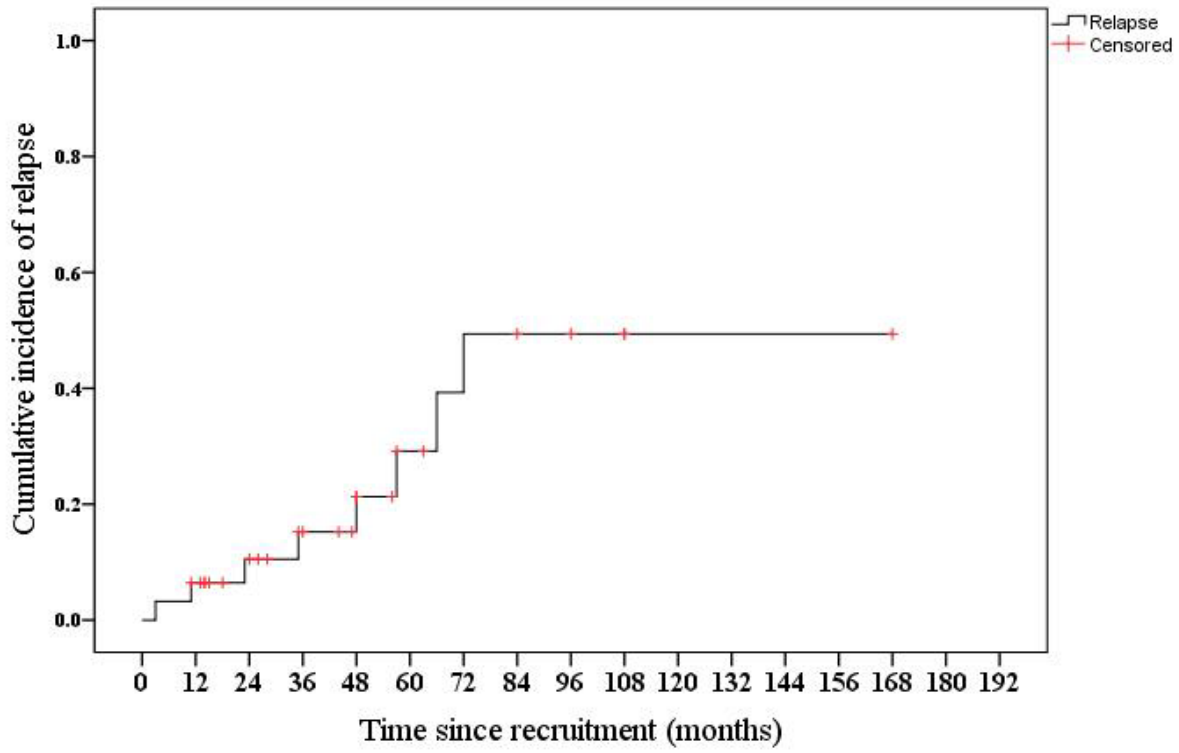


* Follow up duration ≥ 6 months (n=48); vertical dotted line denotes mean time to relapse

Old patients: Among the 40 patients, who had been already consulting us prior to their enrolment in the study, 37 patients had a follow up of ≥ 6 months. Complete/ partial remission was attained at least once for 32 patients (86.5%), while 6 patients never responded to the treatment. The median duration of follow up was 48 (IQR 25-72, range: 11- 168)

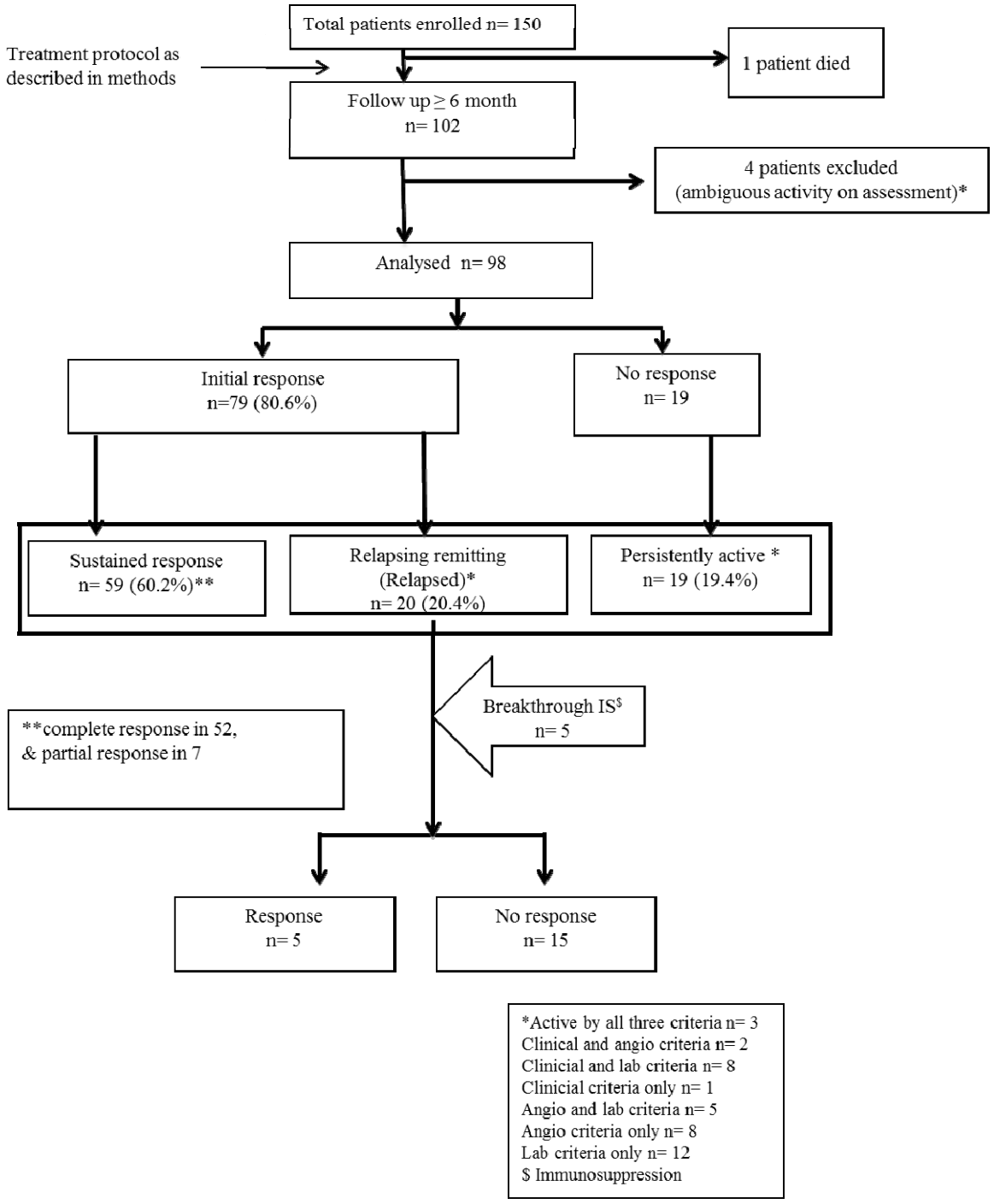
months. Of these 32 patients in remission, 8 of them had relapsed on further follow up with mean time to relapse of 109 (95% CI: 78-141) months, from their baseline visit to our institute at a much earlier period than recruitment in the present study (Figure 13). Time to remission could not be calculated accurately for these patients due to delayed follow up in several of them. The cumulative incidence of predicted relapse at 1 year and 5 years for these patients was estimated to be 10.5% and 28% respectively. Mean steroid dose initiated for these patients was 26.5±14.23 mg/day. However the tapering of steroids for these patients was slower than that in new patients (data not shown).

Figure 13: Cumulative incidence of relapse in 'Old patients'*



* follow up duration ≥ 6 months (n=32)

Figure 14: Flow chart of overall treatment outcome

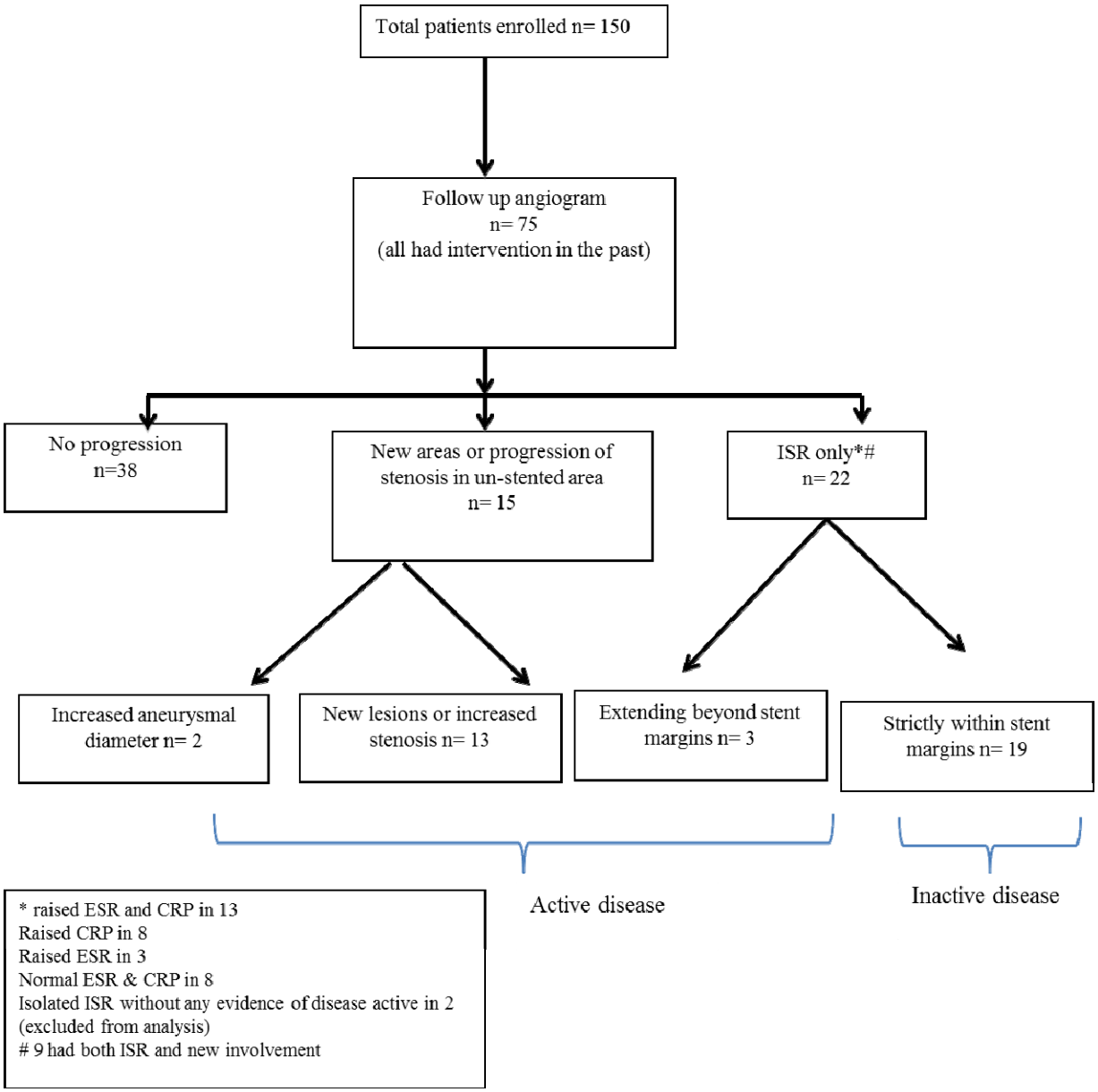


Angiographic outcome (Figure 15): Among 102 patients followed up, 75 had follow up angiography available to assess angiographic progression. Of these 75, only 38 patients (50.6%) had stable disease on angiography without any evidence of new lesions, progressive ectasias, and progression of stenosis or ISR.

Active disease on angiography was noted in 15 patients with 13 having new areas or progression of stenosis in non-stented areas and 2 others had increase in the degree of ectasias.

Evidence of ISR along with additional new areas of stenosis was observed in 9 patients (6 concomitantly, 3 at some other time point), while ISR alone without new areas of involvement was seen in 22 patients. Restenosis was overflowing beyond the stent margins in 3 patients, therefore classifying these 3 patients also as active disease. ISR was associated with concomitant rise in both ESR and CRP, in CRP alone and ESR alone in 13, 8, and 3 patients respectively. Seven patients with evidence of ISR had normal ESR and CRP values.

Figure 15: Flow chart of outcome of interventional procedures



We sought to determine the predictors of angiographic progression including in-stent restenosis. ESR and CRP values at the time of 1st intervention were available for 65 patients with follow up angiography. Raised ESR values at the time of intervention was seen in more number of patients with angiographic progression (19/33) as compared to patients with angiographically stable disease (12/32); but this difference did not reach statistical significance in univariate analysis (p = 0.105). HLA-E genotype *01:01/ *01:01 did not show any association with angiographic progression including new areas involvement, progressed ectasia, and ISR within stented area clubbed together (7/38 vs 12/37, p= 0.16). However, high ESR during intervention was observed to be an independent predictor of angiographic progression during follow up (OR: 7.1, 95% CI = 1.56 –33.3, p= 0.011); on the other hand, HLA-E genotype *01:01/ *01:01 predicted absolutely stable disease without ISR on angiography (OR: 5.8, 95% CI: 1.5 – 23.2, p= 0.013) independent of steroid use, presence of high ESR at the time of 1st intervention, age at onset or disease duration. Steroid dose, second line immunosuppressants, age at onset or disease duration did not influence angiographic outcome.

As mentioned earlier, overall 59 patients were classified as persistent responders, 20 as relapsing-remitting disease and 19 as persistently active disease.

We also noted that none of our patients with type 4 disease had persistently active disease, while significant majority of patients belonging to this angiographic subset had persistently stable disease (0/19, 13/59, p= 0.031). Number of patients with type 4 disease having

relapsing- remitting course were also a negligible minority (2/20, p= 0.3), thereby implying type 4 disease itself as a good responder to treatment with good outcome.

Baseline CRP as predictor of response: The median CRP values at the time of recruitment were significantly lower in those with sustained response ie. persistently stable disease (8.37 ± 11.8 mg/L), as compared to the ones with relapsing-remitting disease (24.5 ± 26.8 mg/L) and persistently active disease (18.2 ± 11.95) (p= 0.017 and 0.005 respectively). The CRP values of those relapsing- remitting disease did not differ significantly from that of persistently active group. The optimal cut off value of baseline CRP which could differentiate sustained responders from persistently active disease group was estimated to be 11 mg/L by ROC curve (AUC=78.4%, sensitivity = 73.7%, sensitivity 75%).

CRP ≥ 11mg/L: Numerically, CRP values ≥ 11mg/L were less frequently observed in sustained responders (n= 17, 28.8%) as compared to the patients with persistently active disease (n= 14, 73.6%) as well as in those with relapsing- remitting disease course (n=8, 40%) with p= 0.001 and p=0.017 respectively. Multivariate analysis too revealed higher CRP values (≥11mg/L) at the time of recruitment as the only independent predictor of persistently active and relapsing disease during follow up with an OR of 5.8 (1.8-19.1, p= 0.004) and 3.4 (1.2- 10.0, p= 0.027) respectively.

CRP between 6 and 10.9 mg/L: On the other hand, 12 out of 13 patients with mild elevation in CRP values (6-10.9 mg/L) at recruitment achieved sustained partial response to treatment; only 1 patient in this subset remained persistently active during follow up.

CRP< 6 mg/L: Thirty five patients had CRP of less than 6 mg/L at baseline. Only 4 out of these 35 patients had persistently active disease by our definition, while 31 patients had persistently stable disease with sustained response during follow up.

Correlation among various parameters of disease activity (Figure 16A-B, Table 9): Even though the raised CRP at baseline predicted a refractoriness to therapy on follow up, a high discordance was noted between the disease activity assessment tools as depicted by ESR, CRP and clinical ITAS 2010 during multiple follow up visits. Simultaneous data was available for ITAS 2010, ESR and CRP for 300 time points for correlation; and, we noted discordance between ITAS and ESR as well as ITAS and CRP on 53.5% and 45% of the occasions respectively.

The correlation of angiography with ITAS 2010, ESR and CRP could be assessed on 111 occasions. Among the time points during which new lesions were observed on angiography (20 occasions in 15 patients), evidence of active disease by clinical ITAS 2010, ESR and CRP, was noted on 50%, 75% and 70% of the occasions respectively. High values of ITAS-A.(CRP), ITAS-2010, ESR and CRP paralleled new lesions on angiography with sensitivity of 68.4%, 50%, 75%, 70% and specificity of 71.9%, 58.2%, 44% and 58.2% respectively.

Figure 16A: Scatter plot between ESR and ITAS 2010*

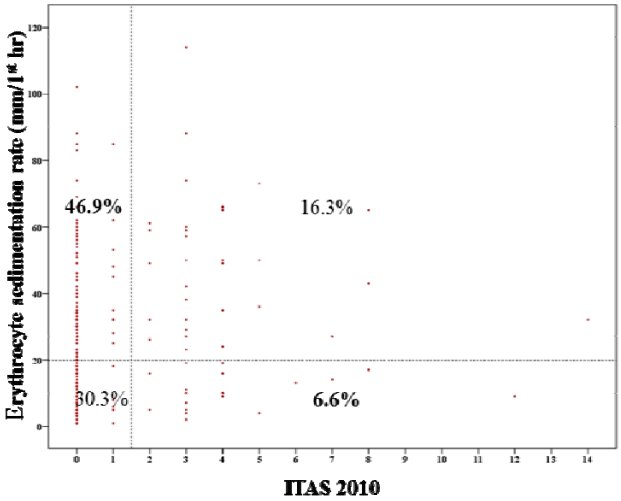
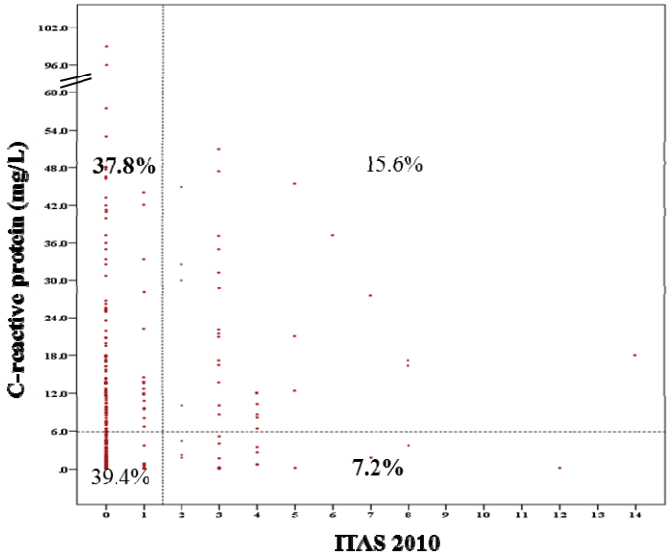


Figure 16B. Scatter plot between CRP and ITAS 2010*



* Horizontal dotted lines in A and B demarcate between normal and elevated ESR and CRP respectively; vertical dotted lines denote the cut off ITAS 2010 value of 2 to differentiate clinical activity versus inactivity.

The distribution of HLA-E genotypes did not differ significantly among the three outcome subsets of patients namely sustained responders, relapsing-remitting disease and persistently active disease. Also, there was no difference in frequency of HLA-E genotypes between patients with angiographically progressed disease versus those without angiographic progression (Table 9 below).

Table 9: Parallel values of ITAS 2010, ITAS-A(CRP), CRP and ESR at the time point of developing new angiographic lesions

Parameter	Value	Angiographic new lesions		Sensitivity	Specificity
		Absent	Present		
CRP	<6mg/L	**47.7%**	5.4%	**70%**	**58.2%**
	>= 6 mg/L	34.2%	**12.6%**		
ESR	<20 mm/1st hr	**36.0%**	4.5%	**75%**	**44%**
	>=20mm/1st hr	45.9%	**13.5%**		
ITAS 2010	<2	**55.0%**	11.7%	**50%**	**58.2%**
	>=2	27.0%	**6.3%**		
ITAS A (CRP)	<3	**61.1%**	7.4%	**68.4%**	**71.9%**
	>=3	21.3%	**10.2%**		

Table 10: Association of HLA-E genotypes with disease outcome in TA

	HLA-E*01:01/*01:01	HLA-E*01:01/*01:03	HLA-E*01:03/*01:03	p
Overall outcome vs genotype				
Persistent repsonders	19	29	11	0.77
Remitting relapsing	6	7	6	
Persistently active	4	11	5	
Angiographic outcome vs HLA-E genotype				
Stable	7	21	10	0.43
Progressed	12	18	7	

Treatment outcome: The disease outcome with various 2nd line immunosuppressants is detailed below in Figure 17. Though mean follow up duration and steroid dose at last follow up was similar among the users of different 2nd line maintenance immunosuppressants , number of patients on azathioprine and methotrexate were negligible as compared to the majority recieving MMf. Any comparison among them, therefore, was not possible. Moreover, a selection bias for methotrexate did exist, as methotrexate was used for TA patients with less extensive disease with relatively lower CRP values as per our treatment protocol or standard of care (Table 11).

Table 11--: Baseline activity and extent of disease in 2nd line immunosuppresant arms

Baseline parameters	Azathioprine (n=12)	Mycophenolate (n=75)	Methotrexate (n=10)
Median DEITAK (IQR)	7 (4-12)	9 (6-13)	8 (5- 10)
Median TADS (IQR)	5 (3-9)	6 (3-10)	6 (5-9)
ESR (mm/1st hour)	29 (20-45)	32 (15-51)	29 (8- 54)
CRP (mg/L)	6 (1.2- 17)	7.9 (2.7-17.0)	5 (1.6-20)

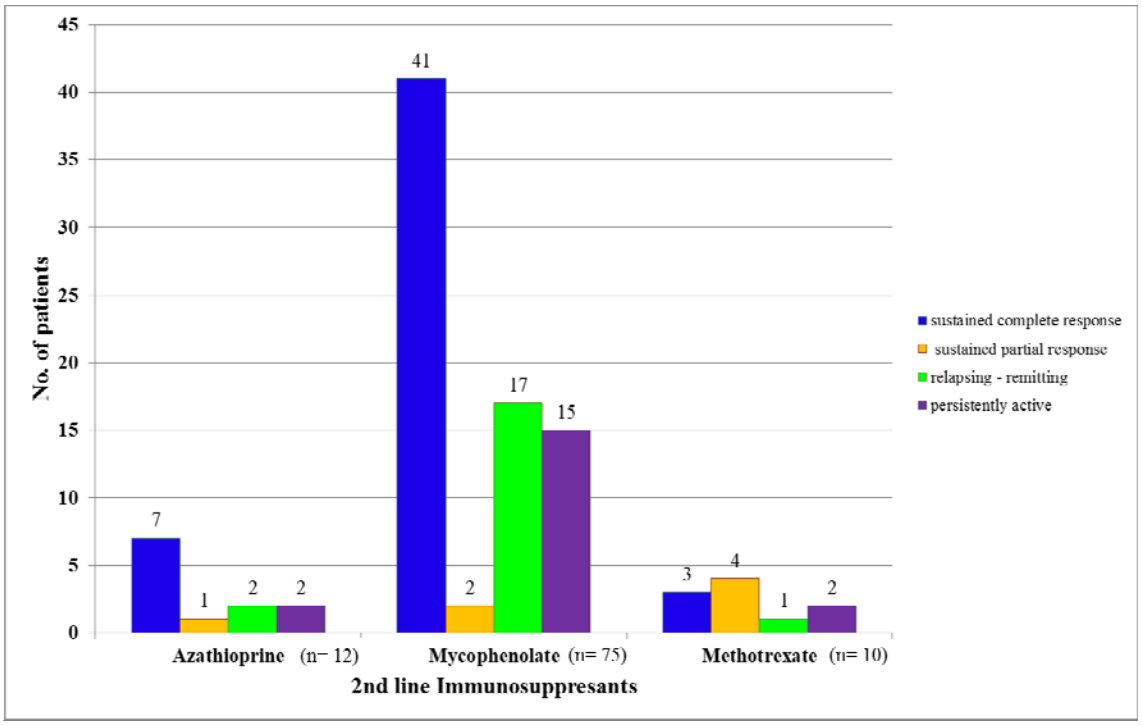
MMf: Among patients initiated on MMf (n=75), initial response was attained in 60/ 75 (80%) patients and it was maintained in 14/23 (60.9%) patients at 24 months. Four out of these 75 patients on MMf , however, recieved breakthrough tocilizumab infusion. In 3 patients, it was given to maintain stent patency as they had preceding history of repeated post intervention ISRs. One more patient received only 2 doses of tocilizumab due to uncontrollable active disease; but this patient developed tuberculosis and hence TCZ had to be discontinued prematurely. One patient was changed from MMf to methotrexate due to financial reasons.

Azathioprine: Among 12 patients on azathioprine, 7 attained sustained complete response (58.3%) and 1 (8.3%) patient had sustained partial response to treatment. Two patients relapsed on follow up, while 2 others did not respond to treatment at all. These 4 patients (33.3%) were switched over to MMf to achieve response as mentioned in the preceding para. In addition, 2 out of the 8 patients with sustained remission opted for mycophenolate during follow up for better safety profile.

Methotrexate: Of the 10 patients on methotrexate, only 3 (30%) had complete response, 4 (40%) had sustained partial response and 1 (10%) patient had relapsed. Two other patients did not attain stable disease throughout the study period. One patient required change over to mycophenolate for maintaining remission.

Numerically, therefore, MMf was superior as 80% of the patients receiving this drug had an initial response and 60.9% of the patients receiving this agent at 24 months continued to have sustained response. Number of patients on azathioprine and methotrexate in our study were too few for any any meaningful conclusion.

Figure 17: Response to second line immunosuppressants in TA



Response to tocilizumab: Overall, 14 patients were given tocilizumab. Ten were initiated on tocilizumab as initial induction agent at recruitment along with steroids ± MMf, while 4 others received it as breakthrough intervention to maintain stent patency in view of repeated ISRs. Complete response was observed in 80% (8 / 10) of the patients recieving tocilizumab as initial induction agent. One other patient on TCZ had partial response and only 1 patient failed to respond to TCZ. On further follow up of the initial responders (complete responders-8 and partial responders-1), the response was sustained in 5 (50%) patients, while 3 patients relapsed following discontinuation of tocilizumab therapy. The follow up was not available for 1 of the initial responders and hence response could not be assessed for this patient.

Last follow up visit:

During the last follow up visit with a median follow up duration of 17 months (IQR: 10-39.5 months), 83 (81.3%) patients were clinically stable with ITAS < 2. In 4 patients with ITAS of ≥ 2, ISRs restricted to stent area alone were the sole contributors towards the score and their ESR /CRP were not raised either; therefore, they were considered to reflect stable disease. ITAS-A (CRP) was less than 2 in 60 patients and <3 in 71 patients at their last follow up visit. Median daily steroid dose was equivalent to 10 (5- 17.5) mg/day of prednisolone; while 61 patients were taking it at ≤ 10mg/day and 43 of them were on ≤ 7.5mg/ day of prednisolone equivalent dose at their last follow up visit.

***Damage at last visit*:** Median TADS at follow up was 7 (IQR: 4-11) with maximum value of 22. New patients had median TADS of 7.5 (IQR: 6-11) at last visit, while old patients' (TADS calculated in 33 patients) median TADS was 5 (3.5-10) at their last visit. Among the

patients with follow up duration of ≥ 6 months, delta TADS could be calculated only for 64 patients with available baseline data for comparison and the median delta TADS value for these 64 patients was 0 (IQR: 0-1; range: 0-9). Of these 64 patients, 4 patients had delta TADS of >1, thirteen patients had delta TADS value =1 and each of the the remaining 47 patients had delta TADS of 0 suggesting no progression of damage during the follow up period in these 47 (73.4%) patients.

Mortality: Among all the patients who were recruited and followed up, only 1 death was observed. The cause of death in this patient was massive cerebral bleed with intra-ventricular and subarachnoid extension immediately following a post-revascularisation procedure.

Discussion

This is the first ever prospective study of HLA-E polymorphism in a large cohort of TA.

This particular polymorphism ie. *rs1264457* has been shown to have functional consequence leading on to altered expression of HLA-E on cell surface by encoding glycine to arginine substitution at position 107 of HLA-E. This may be of immunological significance too as expression of HLA-E, unlike classical MHC Ia, is restricted mainly to the surface of resting T cell, B cells and activated T lymphocytes (62,63) . The other polymorphisms at HLA-E locus are of uncertain significance, except for the case of association of rs2844724 C/T in 3′UTR with coronary artery aneurysm in Kawasaki disease (55).

Results of this study may be summarised as follows: i) HLA-E varaints studied by us are not associated with disease susceptibility in TA, but there seem to be some association with disease phenotype and outcome. ii) Medical treatment was highly successful in our patients with TA and good response was sustained in the majority; refractory disease was observed only in 20.4% of this TA cohort. Progression of damage was also arrested in the majority iii) Angiographic type, inflammatory markers and HLA-E*01:01 genotype could predict outcome of specific subsets in our cohort. iv) Cluster analysis showed symmetrical involvement of contiguous vessels as well as 2 distinct clusters of large arteries in our cohort of TA .

We discuss the commonalities and oddities of our findings in the following paragraphs in the light of published literature and other biological basis.

HLA-E associations with disease: Our work was primarily aimed at studying two major allelic variants of HLA-E namely HLA-E*01:01 and HLA-E*01:03 in Indian patients with TA in order to establish any possible association with disease susceptibility, phenotypic variations as well as prognosis. However, the frequencies of these two alleles was noted to be similar in cases and healthy controls in this study. Even the distirbution of HLA-E genotypes (*01:01 homozygous, heterozygous and *01:03 homozygous) did not differ between cases and controls. Adjusted analysis for sex and geographic origin of patients also showed similar frequencies. The HLA-E*01:01 allele was observed in 51.3% of TA cases and 48.9% of controls; the frequency of HLA-E*01:03 allele was 48.7% and 51.1% in cases and controls respectively. The equal frequency of these two alleles was also observed in Thai (43% vs 57%), South Koreans (49% vs 51%), African- Americans (57% vs 43%), Hispanics (56% vs 44%) and Australians (57% vs 43%) populations (48,50,64,65) . A recent study on south Indian patients with rheumatoid arthritis (RA) also reported similar equal distribution of these two alleles in their cohort of cases as well as healthy controls (52). Grimsely and Ober had explained the phenomenon of near equal distribution of this polymorphism across various populations (50). They had proposed 2 mechanisms : i. A balancing selection during evolution maintains this state of polymorphism as depicted in the preceding instances including our own data or, alternatively ii. The newer allele encoding HLA-E ^{ER} has been "swept to fixation" by selective forces (50). Unequal distribution of these alleles was, however, reported in studies from northern India (70% vs 30%) and Japanese population (32% vs 68%) (50,53); these variations could be due to ethnic diversity, genetic alterations for survival advantage under the prevailing environmental pressures or some other unknown

evolutonary forces playing their role in these populations. Genetic disparities amongst Asian Indian populations of various geographic origins have also been reported in scenarios like frequencies of HLA-B27. In a study from 1170 unrelated healthy Individuals from western India, the prevalence of HLA-B27 positivity ranged from 1.48% to 9.6% among various caste groups, highest being in Marathas. While the frquency was 6% among northern Indian ancestry in one study (66,67), none of the 124 healthy controls from southern Indian population had HLA-B27 allele in another study (68). The present study, however, did not find any significant difference in the distribtuion of the studied HLA-E alleles among the various Indian populations, though our cohort hailed from diverse geographic origin (Table 4, under results) .

In the study on RA as cited above, HLA-E*01:01 and *01:03 variants were also not associated with susceptibility to RA in their south Indian cohort; but the authors noted association of these alleles with treatment response to conventional disease modifiying agents, especially in young onset RA patients. Moreover, a few other studies on RA, bone marrow transplant recipients and type-1 diabetes have also identified this polymorphism as predictor of treatment response or phenotypic variations rather than disease susceptiblity, similar to our results in TA. However, this polymorphism was reported to be associated with disease susceptibility in Behcet's disease and ankylosing spondylitis (48,56).

Subgroup analysis of the patients in the present study, however, showed an independent protective effect of HLA-E*01:01/*01:01 genotype on pulmonary artery involvement (Adjusted OR 0.12, 95% CI- 0.14- 0.98, p= 0.047) and DCMY (Adjusted OR 0.2, 95% CI-

0.05- 1.03, p= 0.055). Although, the frequency of HLA-E*01:01 homozygous genotype was significantly lower in those with pure infra-diaphragmatic (type 4 C-P-) disease as compared to other angiographic subsets (9% vs 31%, p = 0.038), an independent effect was not established in logistic regression (p= 0.069). This near significant effect could be due to small sample size of patients with pure infra-diaphragmatic disease (n=22) and needs further evaluation in a larger study.

HLA-E association with outcome: Our study highlighted HLA-E genotype *01:01/ *01:01 (homozygous state) as a predictor of angiographically stable disease without progression to involve newer vascular areas or ISR (OR: 5.8, 95% CI: 1.5 – 23.2, p= 0.013). This effect was also independent of steroid dose, presence of high ESR and age at onset or disease duration. Apart from predicting angiographically stable disease, HLA-E*01: 01 homozygosity, may also denote a protective role against DCMY as a complication in our cohort. It is also worth mentioning that HLA=E*01:01 allele leads to low expression of surface HLA-E. Thus presence of this allele may result in less effective inhibition of NK cell as well as down-regulation of cytolytic activity by cytotoxic T cells,. Thus, homozygosity for this allele may be associated with a relatively blunted immune response leading to lesser cellular damage and the consequent injury to arterial wall (54).

In an unpublished study on our cohort of TA patients, we have observed significantly higher levels of soluble HLA-E in serum of patients with active TA as compared to stable patients. On serial estimation too, higher sHLA-E level was associated with persistently active or relapsing disease on follow up. A few of these patients and healthy controls from this above

mentioned unpublished study have been genotyped in our present study, thus allowing us to have an idea on the influence of these HLA-E variants on sHLA-E levels. Serum levels of sHLA-E levels were similar in all the 3 HLA-E genotypes studied. The higher serum levels of sHLA-E in active disease may, therefore, be due to increased shedding of this molecule from cell surface under the influence pro-inflammatory mediators as reported earlier (45) and it may not be related to the genotype at all.

Demographic data: As reported in literature, our patients were mostly young adults with median age of 28.5 (22- 36.3) years at presentation. Period of diagnostic delay in our study was similar to that reported in western series, but this delay was less than that reported in several Asian studies (table 11). A Japanese study, however, reported a marked decrease in their diagnostic delay from 5.2 years in pre 1999 era to 1.2 years in patients diagnosed as TA from this millenium (69). The percentage of patients with disease onset at or after 40 years of age in our study was only 10.6%, similar to a recent Japanese series and the NIH series; this figure is, however, lower than most of the other western series. Arnaud etal, in their multi-ethnic cohort of TA patients, noted that 40% of their white patients were older than 40 years of age as compared to only 18.6% of the non-whites (70). Whether these results are due to giant cell arteritis mimicking TA in their cohort remains unanswered, as GCA is the commonest large vessel vasculitis in the western world.

As the duration of symptoms was quite long (33.5 months, range: 12-72 months), our patients had presented with more extensive disease as well as significantly established damage as depicted by high median DEI.TAK score of 9 (Range: 6-13) and high median TADS score of

6 (Range:3-10) respectively. This is also a probable reason for the presence of disease related complications in 35.3% of our patients at presentation. In addition, majority of our patients (60%) had presented with raised CRP, though frequencies of various systemic symptoms ranged only between 17% and 31%. Moreover, subclinical disease activity is a well known phenomenon in TA. Under these circumstances, we used immunosuppressants in the management of most of our patients (Detailed in the subsequent paragraphs).

Contrary to most studies in published literature, female predominance was relatively less prominent in our cohort, with 24.7% of our patients being males. This was similar to previous Indian series (71) and a recent Chinese series (72) with males comprising 21% and 39% of their cohorts respectively. Western data, however, reports males comprising between 3% and 17.1% in various series (21,23,26,27); similar low figures were reported in 2 Japanese series too and only 3.8% and 7% of their TA patients were males (25,69).

The proportion of patients treated for tuberculosis in our series was only 8.7%, which is similar to that reported by Jain etal and a Chinese study (71,72). Lupi-Herrara et al, however, have reported a much higher association of TA with tuberculosis (48%) in their cohort of patients (22).

All the other demographic features in our cohort were similar to that described in literature, except for a higher frequency of renal artery stenosis (52.5%) in our cohort. A similar prevalence was, however, reported in earlier series from India and Mexico (22,71).

Outcome of medical treatment: Majority of patients (146/150) were initiated on steroids and 2nd line immunosuppressant in our study. MMf was the most commonly used 2nd line cytotoxic (79.5%) in our cohort.

Response to treatment was observed in 80.6% of our patients and it was sustained in 60.2% over the median follow up period of 17 (IQR 10-35) months. Only 20.4% of our patients experienced relapse, which is much lower than that reported in the two US cohorts (NIH series- 80%, Mayo clinic- 46%) and a recent Japanese series (70%) (Table12) (26,27,69). Moreover at the last follow up visit 81.3% of our patients were clinically stable with an ITAS score <2 at a median steroid dose of 10 (5-17.5) mg/day.

Among the patients on MMf, 77.3% (n=58) attained complete response and 2.7% (n=2) had a partial response. Response was sustained in 80% (n=49) for 1 year and 14/23 (60.9%) patients at 24 months. We had 12 patients on azathioprine, of which, 75% (n=9) had complete response and 8.3% (n=1) had partial response. This response was sustained in 80% (n=8) through their entire follow up. Azathioprine along with steroids has also been used with success in a smaller cohort of 15 TA patients from Northern India with 100% improvement in all patients at 12 months of follow up (73). These results are better than 50% sustained response previously reported with methotrexate by Hoffman etal (31). However, small number of patients, both in our cohort as well as in the North Indian cohort, doesnot permit us to draw loud conclusions regarding azathioprine's efficacy in TA.

On the hand, only 30% of our patients on methotrexate achieved sustained response and another 40% had partial response with persistently elevated CRP, even though clinical ITAS

score remained at less than 2. This is in-spite of our policy of using methotrexate in less severe disease without major complications at presentation. We had to, however, use methotrexate in patients with raised inflammatory markers too at times, when financial constraints of the patient was an issue. Patients who could not afford azathioprine or mycophenolate was given methotrexate irrespective of the disease activity status. Again, smaller number of patients on methotrexate was a limiting factor for any concluding evidence in favour of methotrexate in TA.

In a recent French series, the authors reported unsatisfactory treatment response in 46% of patients with TA. Majority of their patients were on either azathioprine or methotrexate. MMf was used in only 7.3% of TA patients as the last option in this French cohort and hence its efficacy cannot be commented upon in their study (70). Our current standard of care with MMf as the preferred 2nd line agent of choice is because of its very high safety profile with its efficacy comparable, if not superior, to azathioprine. We did not come across any serious adverse event with the use of MMf in 75 patients under our follow up, where as life-threatening cytopenia was noted even within our small cohort of patients on azathioprine (n=12).

Altogether, 14 of our patients received biological agent, namely tocilizumab (TCZ); 10 patients received it as initial induction agent along with steroids ± MMf and 4 others received it as breakthrough intervention to maintain stent patency in view of repeated ISRs. Complete response was observed in 80% (8 / 10) of the patients receiving tocilizumab as initial induction agent. One other patient on TCZ had partial response and only 1 patient

failed to respond to TCZ. On further follow up of the initial responders (complete responders-8 and partial responders-1), the response was sustained in 5 (50%) patients, while 3 patients relapsed following discontinuation of tocilizumab therapy. The follow up was not available for 1 of the initial responders and hence response could not be assessed for this patient. These results are more or less similar to the reported findings in previous studies (74,75). Anti-TNF agents were not used in any of our patients due to financial constraints as well as the concern regarding latent tuberculosis status in a country with a high prevalence of tuberculosis. However these agents are being reported to be promising as shown in the study from Cleveland clinic, USA. Of the 11 patients receiving TNF blockers, 6 patients achieved sustained remission, 2 were lost to follow up and 3 had relapsed over a median follow up of 26 month (Range: 3 months to 6 years) (21). Recently, a study on 9 patients with TA on biologicals showed a sustained response on serial monitoring in >90% of patients on continued therapy with either TNF blockers or tocilizumab. In this study, authors have concluded that biological agents may be considered as upfront therapy in some patients with TA to cut down the dose of steroids (76).

Comparison with previous major series reporting outcome in TA patients (Table 12):

The use of steroids in management of TA was only 7% and 16% in older series from Mexico and India, while it has been higher in data from developed countries. Steroids were used in 95.3% and 2nd line immunosuppresants in 97.3% of our patients. Response to immunosuppression ranges from 60% to 96% across all these studies. However, a recent Japanese series has reported only 35% response. This could be due to a long diagnostic delay

in that study, rendering their patients progress to advanced damage, as damage is less susceptible to treatment unlike disease activity.

Second line immunosuppresants in TA has also gained increased acceptance in recent time as compared to past. Earlier reports from Mexico, Japan and India reveal only 1/106 patient recieving 2nd line immunosuppressants, in contrast to their use in >60% of TA patients in the recently published series from France and USA (22,25,26,31,70,71). Majority (97.3%) of the patients in our cohort received these agents. This may be the single most important reason for lower relapse (20.4%) in our study, as compared to that reported in studies from NIH (80% over a median follow up of 5.3 years), Cleveland Clinic Foundation, USA (96% over a follow up period of 3 years), Japan (70% over 0.5-5 years) and Mayo clinic, USA (46% cumulative relapse at 5 year). Cumulative incidence of relapse at 5 year estimated by KM curve for our old patients' subset with longer follow up is 28%, much lower than all these series. Moreover, our policy of slow tapering of steroids as compared to a relatively faster tapering approach practised in the western world may be an additional contributor towards a lower relapse rate. In fact, Ohigashi et al, in their recent study, have observed mean dose reduction rate of steroids to be the only predictor of relapse in their cohort of TA (69). In their study, a relapse rate of 59.1% was observed for patients who had a steroid reduction rate >1.2 mg/month as compared to 0% in those with steroid reduction rate <1.2mg/ month. Thus, we can safely conclude that medical management of TA patients has changed towards a more aggressive immunosuppressive approach in the present era. Universal use of maintenance

immunosuppresants has led to lesser relapses in this medical condition which was a rule in the recent past.

Predictors of outcome: CRP values > 11mg/L at presentation predicted persistently active (refractory) disease as well as relapsing and remitting course in our study with odds ratios of 5.8 and 3.4 respectively. Type 4 disease was the single most angiographic subset which did not have persistently active disease course. We, therefore, suspect TA patients belonging to angiographic subset other than type 4 as well as those presenting with high CRP values (>11 mg/L) needs to be treated with more aggressive immunosuppression than the rest. To the best of our knowledge, the only other predictors of higher relapse rate reported in literature include high ESR as well as younger age at diagnosis (77).

Interventions: A high proportion of our patients (68.6%) underwent revascularisation procedures, mainly endovascular re-vascularisation and stent insertion (97%). Our figure is higher than the data from Chinese series and the western data from the US, France and Italy. However, as seen in the comparative table below (table11), these procedures are being performed more often in the most recent studies than the earlier Mexican, Indian and Japanese series. As mentioned above, revascularisation procedures comprised the bulk of the endovascular procedures in our study. At the last follow up visit, sustained patency of vessels after endovascular revascularisation procedures in our series was 59.7%, which is comparable to the 64% success rate of arterial bypass/ graft procedures achieved at CCF, USA; but their 22% success rate with angioplasty is much inferior to our intervention results mentioned above.

Altogether 101 out of 150 patients in our cohort had undergone endovascular revascularisation (ER) procedures with or without stent placement. Repeat imaging was available for 75 patients to assess the vascular patency of the intervened areas. Immediate success rate of ER was good in our cohort, but subsequent in-stent restenosis was observed in 41.3% (n=31) during follow up. Previous series from different parts of world have also reported high rate of restenosis following endovascular procedures ranging between 17% and 60% at 5 years' follow up. The restenosis rates for endovascular procedures have been uniformly reported to be higher as compared to bypass/ graft procedures. Restenosis following endovascular interventions are, however, lower in our series as compared to ones from China (77%) and France (64%), but similar to that reported in a study from Cleveland clinic foundation, USA (32% at 4 years) (21,70,72). The same US study showed a higher post angioplasty restenosis over 12 year follow up period (21). One study from UK has shown long term patency rate of 52% at 5.9 years following angioplasty (78). The outcome of surgical revascularisation procedures in our study has not been discussed here, as we had only 2 patients who underwent bypass or arterial graft procedures. The differences in sustained success rate of endovascular procedure across various series could be due to differences in the approach to prior medical therapy, follow up duration, techniques of interventions used, ethnicity and genetic make up of the patients. Raised ESR at the time of intervention was associated with higher odds of angiographic progression and ISR on follow up in our study (OR: 7.1, 95% CI = 1.56 – 33.3, p= 0.011). Biological inflammation has been observed to be associated with complication after revascularisation in a previously published study. In that study, Saadoun et al have observed higher CRP values ($p< 0.001$), higher ESR

($p<0.001$) and higher fibrinogen ($p< 0.005$) to be associated with complications after revascularisation (79). Injury to the endothelium due to barotrauma, manipulation and metallic stent deployed during procedure may itself incite inflammation and reparative fibrotic responses and beget eventual restenosis of intervened area, rather than due to any progression of inherent disease activity. Ohigashi etal (Japan) have observed a reduction in restenosis rate, when surgical treatment was performed during the inactive stage of the disease, and when the patient was treated with both glucocorticoids and 2nd line immunosuppressive agents (69). Use of steroid (95.3%) and 2nd line immunosuppressive agents (97.3%) in the vast majority of our patients could possibly be one of the reasons for better patency rates in our cohort (69).

Subclinical disease: Among the patients with active disease during follow up (n=39) i.e. those with relapses as well as persistent disease activity, activity was evident by clinical ITAS or ITAS-A in 79.5% (n=31) of them. Eight others (20.5%) was presumed to have subclinical activity as disease activity was evident only by angiographic progression (Flow chart in results section). Laboratory evidence of activity in the form of raised CRP was present in 12 out of 31 patients with activity as defined by ITAS / ITAS-A. These 12 patients' positive ITAS-A were solely contributed by raised CRP values alone at least at 2 time points in absence of any clinical score. Among relapsed patients (n=20), 4 were clinically quiescent. We attribute subclinical activity as explanation for relapse in these 4 patients too, as new areas of vessel involvement was documented by angiography in these patients in absence of any clinical finding. Discordance between inflammatory markers and histologic

assessment of activity is a known phenomenon in upto 1/3rd of TA as observed previously in other studies (21,26,27). Our study too has noted this phenomenon, as figure-16 and table-9 under the results section depicts discordance between CRP/ESR, ITAS and angiographic activity . It further reinforces the existing notion that acute phase reactants alone can not reflect disease activity in a significant proportion of TA patients. ITAS-A (CRP) , however, had lower discordance and performed somewhat better in this regard. Our study, therefore, reiterates the need for meticulous surveillance including follow up vascular imaging, especially in the subset with ambiguous disease activity.

Mortality in TA has been steadily decreasing over the past decade as per the recent reports (Table 11). In one of the landmark papers, Ishikawa et al in their analysis of 120 patients had identified the following 5 factors as predictors of mortality: a) presence of major complications b) progressive disease course c) Age >35 years d) longer delay between symptom onset and diagnosis e) patients presenting before 1975 in their series. The reason for better survival in recent times could be the shorter time to diagnosis, use of immunosuppresants in a larger proportion of patients as well as interventions at appropriate time to prevent ischaemic complications (25). A reassuring point in our study was very low mortality with only one death in our series. However the mean follow up duration of our study was relatively shorter to extrapolate the data. We could, however, arrest progression of damage in our patients with median delta TADS of 0 (0-1) at a median follow up period of 17 months. More than 2 unit increment in TADS was seen in only 4 patients and was mainly contributed by in-stent restenosis and repeated angiographic procedures. This is again a

reminder that intervention induced biological inflammation, rather than true disease activity is a reality. These results are similar to the data of our previous unpublished study, where delta TADS was calculated retrospectively (80).

The response rates reported in various studies cannot be compared to draw any definite conclusion due to heterogenicity in definitions of outcome. For example, in a study by Schmidt et al, sustained remission was defined as remission for a period of 6 months with prednisolone dose <10mg/day, while we defined sustained remission as maintenance of remission till the last follow up without relapses in between. Secondly, delay in diagnosis has a bearing on outcome of patients.

Cluster analysis: Lastly, we also studied the pattern of vascular involvement by performing cluster analysis. Similar to previous two studies, the results of cluster analysis in our cohort showed symmetrical distribution of lesions in all the arteries except for slight asymmetry in occurrence of vertebral and subclavian artery lesions, left subclavian being more frequently (62%) involved than right (46%). Asymmetry in subclavian artery involvement has been reported in data from VRCC cohort of TA as well, but not in the study by Arnaud et al. We also observed a contiguous involvement of vascular areas as shown by clustering of aortic arch, ascending aorta and descending thoracic aorta, and a correlation between involvement of common carotids, vertebral and subclavian arteries. We also observed a clustering of right subclavian and & left common carotids. At a cut off distance of 0.55, we observed two broad clusters. Cluster 1 comprising of coronary artery, infra-diaphragmatic aorta and its branches, while cluster 2 involved supra-diaphragmatic aorta and its branches. Subclavian and carotid

artery clustering has been reported in VRCC cohort study. But we did not find thoracic descending aorta clustering with abdominal aorta as noted in the VRCC cohort as well as another earlier study by Arnaud etal (81). Biologically, the abdominal aorta is different from thoracic aorta in many aspects. Phylogenetically, smooth muscle cells (SMCs) of descending thoracic aorta along with aortic trunk, proximal arch, pulmonary arteries originate from neural crest, but abdominal aorta and more distal part of aorta derive the SMCs from mesoderm (82) . Unique genetic programming is postulated to be responsible for differential responses of these SMCs to cytokine stimulation and thus may explain lack of clustering of thoracic aorta with abdominal aorta in our study. Similar to abdominal aorta, the coronary arteries also possess SMCs of mesodermal origin thus explaining our apparently unusual cluster of infra-diaphragmatic disease with coronaries.

This finding along with our results on genotyping and outcome analysis reiterates that infra-diaphragmatic TA could be a condition distinct from other subsets of TA. IgG4 related diseases should also be ruled out in type 4 TA due to characteristic site of involvement. However, this paradoxical appearing clustering of coronaries with infra-diaphragmatic disease cannot be fully explained at present, although embryological origins as described above may be a possibility. As stated in earlier studies, results of cluster analysis may also vary if different statistical methods are used.

Table 11: Comparison of large TA series across continents

Region	Mexico (Lupi-Herrara, 1977)[22]	Japan (Ishikawa, 1994)[25]	NIH (Kerr, 1994)[27]	India (Jain, 1996)[71]	Italy (Vanoli, 2005)[23]	CCF[b], USA (Maskowmich, 2007)[21]	France (Arnaud L, 2010)[70]	Japan (Ohigashi, 2012)[69]	USA (Schimdt, 2013)[26]	China (Yang L, 2014)[72]	India (Present study, 2015)
Design [a]	R	P	P	R	R	R	R	R	R	R	P
Period	1955- 74	1957-90	1970-90	NR	1995-97	1992- 2004	1995-2006	2000- 2010	1984-2009	2002-13	2012-2014
No. of patients	107	120	60	106	104	75	82	106	126	556	150
Baseline demography and characteristics											
Females	84%	93%	97%	61%	87.5%	91%	82.9%	96.2%	91%	79%	75.3%
Age at onset (years)	11-30	30*	25 (7-64)	27*	29.2*	26 (5–49)	30.2 (9-66)	26.9±11.8	29.2 (20.5-34.5)	28.9± 12.0	24 (6-58)
Age at onset ≥40 years	Excluded	<29%#	13%	17.3%	17%	NR	32%	13.2%	25%	19.4%	10.6%
Diagnostic delay (months)	12-288	58.8 (1 -484)	10 (0-156)	NR	15.5 (0-325)	NR	6.0 (1-220)	39.6 ± 60	17.5 (7-41.8)	91.2± 4.2	12 (IQR 6-36)
Type 5 ds	65%	NR	68%	55.7%	53%	NR	38.5%	43.4%	54%	37.8%	57%
C+ disease	9%	NR	ND	NR	NR	12%	NR	8.5%	22% (n=4)	11.7%	27%
P+ disease	14%	NR	100% (4/4)	49.% (n=4)	3/9	7%	12.2%	4.7%	33% (n=6)	14.7%	15.1%
Renal Artery	62%	NR	38%	53%	34.4%	18%	NR	21.7%	21%	35.5%	52.5%
History of TB	48%	NR	NR	7.5%	NR	NR	NR	NR	NR	7.2%	8.7%
Claudication	29%	NR	62%	NR	58.6%	48%	45.1%	NR	52%	28.4%	57%
Pulse loss	96%	NR	53%	NR	75%	57%	53.7%	38%	70%	NR	57%
Fever	18%	NR	27%	16%	50%	35%	<35%	39%	29%	9.2%	25%
Raised ESR/CRP	83%	76.7%	72%	60%	87%	85.5%	57%	NR	71%	23.1%	60% (CRP)
Disease activity criteria	Nil	NR	NIH	ND	NIH	NIH	NIH	NR	NIH	NIH	ITAS
Treatment details											
Steroids	7%	80%	80%	16%	86%	93%	96.1%	79.2%	92%	85.9%	95.3%
2nd line immunosuppressant	NR	NR	41.7%	n=1	54%	73%	66.3%	18.9%	66%	4.1%	97.3%
Vascular Intervention	8.5%	12%	50% (36%)[h]	7.5%	50%	48%	48.8% (27.5%)[h]	22.6%	55%	82.9% (48.5%)[h]	68.6%
Follow up data											
Follow up	NR	ND	75%	65%	ND	40%	NR	33%	63%	58.7%	68% , 22% at year
Follow up duration (yrs)	NR	13	5.3 (0.5 - 20)	NR	ND	3.0 (0.3 - 10)	NR	0.5–5	5.5 (IQR:2.9-10)	5.0 ± 0.2	1.4 (IQR- 0.8-3.3)
Response to treatment	2/107 [C]	NR	60%	5/16 [C]	NR	93%	NR	35%	96%	NR	80.6%
Relapse (%)	NR	NR	45, >80 [d]	NR	NR	96	NR	70	46 (at 5yrs)	NR	20.4 (28 at 5 yrs[g])
Restenosis post intervention	33%	NR	NR	NR	NR	78%[e] , 36% [f]	NR	12–71.4%	NR	NR	41.3%
Mortality (n) / study duration (years)	15/ 19 years	13 (16%) /13	3% (n=2)	17.3% (n=12)	NR	4% (n= 3) / 3	8.6% (n=8)		4.8% (n=6) / 15	5.7% (n= 32) / 5	0.7% (n=1) / 2

*Mean age; [#] % of patients >35 years of age ; [a]R- retrospective, P – prospective; [b]Cleveland clinic foundation, USA; [c]patients in remission/ no. treated with immunosuppression, [d] clinical , angiographic relapse; [e]post endovascular procedure, [f]post bypass/graft procedure, [g]old patients group only, [h]bypass/ graft procedures

Our study has many strengths. Our large cohort of patients and controls was adequate to perform such a genetic study in this rare disease. This is also the first ever study on HLA-E polymorphism in TA and its associations with disease phenotype and outcome. Only a handful of TA series from Japan and NIH in the past had description of prospectively collected data. In our series, we enrolled 110 patients prospectively, while only 40 patients had their baseline details collected retrospectively. Even these 40 patients, who belonged to old patients group, had a prospective follow up for 2 years i.e. during the study period. One hundred and forty four out of 150 patients in our cohort had baseline angiographic data and large proportion of patients on follow up (75/102) had follow up angiography to delineate disease status at follow up without ambiguity. This is also the first study to use a damage index (TADS) for objective assessment of damage progression.

Our cases and controls were not matched for sex and region of geographic origin . Our stratified analysis for sex and region also did not show any difference in the genotyping results. There was also no difference in the allele frequency across patients from various geographic regions from India. We were limited by a short follow up duration for our new patients, as it is a prospective data and patients are continuing to be under follow up. However, our patients belonging to old patient group (n=40) had a relatively longer follow up.

In a nutshell, results of the primary objective in our study revealed no overall association of HLA-E* 01:01 and HLA-E *01:03 with TA, thereby ruling out any role of these variants in conferring susceptibility to disease in TA. However, the studied variants may have some

associations with subsets of TA with prognostic significance and they may define outcome. Powered studies designed for specific subsets and specific outcome as primary objectives may shed more light in these aspects.

Our finding of good outcome with aggressive immunosuppression, objective assessment and follow up, however, is reassuring; ‘mantra’ for successful treatment in TA may be just that.

Conclusions

1. Frequencies of HLA-E variants *01:01 and *01:03 were similar in TA as well as healthy controls in our study, thereby these variants may not confer any disease susceptibility risk in Asian Indian patients with TA.

2. HLA-E*01:01 homozygous genotype was protective against pulmonary involvement and occurrence of DCMY as complications in our cohort.

3. A. Of the 80.6% of our TA patients with initial response to therapy, 60.2% could sustain this benefit at 24 months, while 20.4% had relapsing- remitting course. Therefore, only 19.4% of our patients failed to respond with medical treatment protocol followed by us.

   B. Pure infra-diaphragmatic disease was consistently associated with sustained response to medical treatment. CRP values less than 11mg/L at baseline was observed to be an independent predictor of sustained response, while HLA-E*01:01 homozygous genotype and normal ESR values at the time of intervention predicted angiographically stable disease without any ISR during follow up of our cohort.

4. In our cohort, damage progression could be arrested in majority with our treatment protocol as reflected by no increment in TADS in the majority.

5. Cluster analysis of involved vessels in our study patients revealed:

i. Symmetrical disease

ii. Contiguous vessel involvement

iii. Two broad clusters emerged:

   a. Pure infra-diaphragmatic disease with coronary involvement

      and

   b. Supra-diaphragmatic disease.

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Annexure -1a

DEI.Tak – Disease Extent Index for Takayasu's Arteritis

Patient name:

Tick Box only if abnormality is present (new or worse within 6/12), with duration for each symptom.
Tick box only if abnormality is attributed to current vasculitis.

Visit Date :
Investigator:

	PRESENT	duration
1. SYSTEMIC		
None	☐	
Malaise/Wt. Loss>2Kg	○	
Myalgia/Arthralgia/Arthritis.	○	
Headache	○	
Fever	○	
2. CUTANEOUS		
None	☐	
Gangrene	○	
Other Skin Vasculitis	○	
3. MUCOUS MEMBRANES		
none	☐	
Present	○	
4. EYES		
None	☐	
Blurred Vision	○	
Sudden Vision Loss	○	
Other	○	
5. ENT		
None	☐	
Present	○	
6. CHEST		
None Persistent	☐	
Cough	○	
Dyspnea/Wheeze	○	
Hemoptysis/Hemorrhage	○	
Massive Hemoptysis	○	
Respiratory Failure	○	
Chest Radiology	○	
Active Vasculitis confirmed	○	

	PRESENT	duration
8. ABDOMEN		
None	☐	
Severe Abdominal Pain	○	
Bloody Diarrhea	○	
Gut Perforation/Infarct	○	
Surgical Opinion / tests	○	
Active Vasculitis confirmed	○	
9. RENAL	☐	
None		
Hypertension (Diastole >90)	○	
"" Systolic >140	○	
Proteinuria (>1+/0.2g/24H)	○	
Hematuria (>1+/10RBC/ml)	○	
Creatinine (125-249 μmol/L)	○	
Creatinine (250-499 μmol/L)	○	
Creatinine (>500 μmol/L)	○	
Rise in creatinine >30% or > 25% fall in creatinine clearance.	○	
10. Nervous System		
None	☐	
Organic Confusion/Dementia	○	
Seizures (not hypertensive)	○	
Stroke	○	
Syncope	○	
Cord Lesion	○	
11. . Genitourinary System	☐	
None		
Sexual Impotence	○	
Abortions	○	

7. CARDIOVASCULAR SYSTEM

none ☐

Bruits (see 7a) ○
Pulse Inequality (See 7b) ○
Pulse Loss (See 7c) ○
Pulse Loss with threatened loss of limb. ○
Claudication (See7d) ○
Carotidodynia ○
Aortic Incompetence ○
Pericardial Pain/Rub ○
Ischemic Cardiac Pain ○
Congestive Cardiac Failure ○

Cardiology Opinion/Tests

Active Vasculitis confirmed ○
Pericarditis ○
Myocardial Infarct/Angina
Cardiomyopathy

7a. Bruits	**R**		**L**
Carotid	○		○
Vertebral	○		○
Subclavian	○		○
Renal	○		○
Abdominal		○	
Inguinal	○		○

7b. Pulse and BP Inequality

Present ○

7c. Pulse Loss

Carotid	○		○
Subclavian	○		○
Brachial Radial	○		○
Femoral Popliteal	○		○
Posterior Tibial	○		○
Dorsalis Pedis	○		○
	○		○

7d. Claudication

	○		○
Arm		○	
Leg		○	
Neck			

13. PGO (Active / Grumbling or persistent / Inactive): ○

12. Other Vasc items:

ESR **CRP**

Revised form by M.R Sivakumar, R.Misra, and P.A.Bacon – Dec 2005

Annexure-1b

ITAS2010 – IndianTakayasu's Arteritis Activity Score

Tick Box only if abnormality is present and new or worse within the past 3/12.

Tick box only if abnormality is ascribed to current, active vasculitis.

Name:
Unit Number: Visit Date:
Investigator:

PRESENT

1. SYSTEMIC
None ☐
Malaise/Wt. Loss>2Kg ○
Myalgia/Arthralgia/Arthritis. ○
Headache ○

2. ABDOMEN
None ☐
Severe Abdominal Pain ○

3. Genitourinary System
None ☐
Abortions ○

PRESENT

4. RENAL
None ☐
Hypertension (Diastole >90) ⊡
"" Systolic >140 ○

5. Nervous System
None ☐
Stroke ⊡
Seizures (not hypertensive) ○
Syncope ○
Vertigo/dizzyness ○

6. CARDIOVASCULAR SYSTEM

none ☐

Bruits (see 6a) ⊡
Pulse Inequality (See 6 b) ⊡
New Loss of Pulses (See 6c) ⊡
Claudication (See 6d) ⊡
Carotidodynia ⊡

Aortic Incompetence ○
Myocardial Infarct/Angina ○
Cardiomyopathy/cardiac failure ○

6a. Bruits

	R	L
Carotid	○	○
Subclavian	○	○
Renal	○	○

6b. Pulse and BP Inequality
Present ○

6c. Pulse Loss

Carotid	○	○
Subclavian	○	○
Brachial	○	○
Radial	○	○
Femoral	○	○
Popliteal	○	○
Posterior Tibial	○	○
Dorsalis Pedis	○	○

6d. Claudication
Arm ○
Leg ○

Other Vasculitis items:

ESR **CRP**

Item scores ☐ **= 0** ○ **= 1** ⊡ **= 2**

Scoring ITAS2010 : Add all scores. In CVS , if both boxed circle and circle are ticked, add both (see glossary) **.**

Scoring ITAS.A including acute phase response

- for ESR, score ITAS plus: 0 for <20; 1 for ESR 21-39; 2 for ESR 40- 59; and 3 for >60 mm ESR /hr
- for CRP score ITAS plus: 0 for CRP <5; 1 for CRP 6-10; 2 for CRP 11-20; and 3 for >20 mg/dl

Physician Global Assessment

Active / Grumbling or persistent / Inactive

New Imaging Y / N? If Y - specify _____

ITAS2010 form. M.R Sivakumar, R.Misra, D.Danda & P.A.Bacon - Mar'10
ITAS.A form – ibid Oct 2012

Annexure - 1c

TADS – Takayasu's Arteritis Damage Score (Short form)

Record any abnormality that has occurred since the onset of aorto-arteritis currently present or not, as this is a cumulative damage score

Tick Box only if abnormality present for at least 6/12.

Name or # :
Visit Date :
Investigator:

	PRESENT
1. EYES	
None	☐
Visual Loss in one eye	○
Vision Loss in second eye	○
2. CHEST	
None	☐
Persistent Cough Dyspnoea/Wheeze	○
Respiratory Failure	○
3. RENAL	
None	☐
Diastolic BP >95 [sic] requiring	○
Systolic BP >140 [sic] requiring	○
Proteinuria (>1+/0.2g/24H)	○
Creatinine >150	○
End-stage renal failure)	○

	PRESENT
4. NERVOUS SYSTEM	
None	☐
Organic Confusion/Dementia	○
Seizures (not hypertensive)	○
Stroke	○
2nd Stroke	○
Cord Lesion	○
5. Drug-related and other damage	
None	☐
Malignancy	○
Infertility	○
Other	○
6. Vascular Interventions	
None	☐
First dilatation, stent or surgery	○
2nd procedure	○
Blockage/restenosis of above	○
Second stent/etc.	○

7. CARDIOVASCULAR SYSTEM
None ☐

		R	L
Bruits	○	2nd Bruits	○
Pulse and B.P. Inequality	○	**7a. Pulse Loss**	
Pulse Loss (See 7a)	○	Carotid	○ ○
Claudication (See 7b)	○	Brachial	○ ○
Aortic Incompetence	○	Radial	○ ○
Ischemic Cardiac Pain	○	Femoral	○ ○
Congestive Cardiac Failure	○	Popliteal	○ ○
Cardiomyopathy	○	Posterior Tibial/Dorsalis Pedis	○
		7b. Claudication	
		Arm or leg	○

8. Other Damage Items

TADS short form M.R. Sivakumar, R. Misra, & P.A. Pecoul – Nov 2010

Annexure 2a: Clinical Records Form

Study Title: HLA-E in Takayasu arteritis

Baseline visit: **Serial.no.**

Date of recruitment/ sample collection:

Patient ID: Sex: Male /Female

Address: Phone no.:

Date of symptom onset: Date of diagnosis:

Duration of symptoms prior to 1st visit (months): Delay in diagnosis:

Age (years): Age of disease onset (years):

Outside diagnosis:

Co morbidities: y/n Diabetes mellitus: y/n

Coronary heart disease: y/n Bronchial asthma: y/n

Old Tuberculosis: y/n Active tuberculosis: y/n

Others:

Family history:

Angiographic type of disease:

Coronary involvement: y/n Pulmonary involvement: y/n

Disease extent:

Coronaries: y/n Extent:----------

Right internal carotid: y/n Extent:----------

Right internal carotid: y/n Extent:----------

Left internal carotid: y/n Extent:----------

Right common carotid: y/n Extent:----------

Right subclavian: y/n Extent:----------

Left subclavian: y/n Extent:----------
-

Right vertebral artery: y/n Extent:----------

Left vertebral artery: y/n Extent:----------

Right brachiocephalic: y/n Extent:----------

Right brachiocephalic : y/n Extent:----------

Ascending aorta: y/n Extent:----------

Ascending aorta: y/n Extent:----------

Arch: y/n Extent:----------

Descending thoracic aorta: y/n Extent:----------

Abdominal aorta: y/n Extent:----------

Coeliac artery: y/n Extent:----------

SMA: y/n Extent:----------

IMA: y/n Extent:----------

Right Renal: y/n Extent:----------

Left Renal: y/n Extent:----------

Right CIA: y/n Extent:----------

Left CIA: y/n Extent:----------

Others:

Aneurysms: y/n Stenosis: y/n Occlusion: y/n

Height (cms): Weight (kgs):

Presenting symptoms: ----------

Malaise: y/n Fatigue: y/n

Weight loss: y/n Fever: y/n

Gangrene/ skin vasculitis: y/n Mucous membrane inv: y/n

Claudication: y/n Visual: y/n Permanent visual loss: y/n

Headache: y/n Syncope: CVA:

Cardiac: y/n Cardiac specify:----------

Abdominal pain: y/n Dyspnea: y/n

Chest pain: y/n Raised creatinine: y/n

Systolic Hypertension: y/n Diastolic Hypertension: y/n

Carotidodynia: y/n

Others: ----------

Absent pulse: y/n

Absent pulse name: ----------

Bruit: y/n

Bruit region:

DEITAK: ITAS: TADS:

ESR in mm/hr: CRP in mg/l: ITAS A:

Kerr score: PGO:

Hb in gms: TC in /mm3:

Other investigations: ----------

Imaging: ----------

Prior aspirin: y/n Prior statins: y/n

Prior antihypertensive: y/n Prior steroid dose in mg/day:

Prior immunosuppressant: none (choices can be aza/ cyclo/ mmf/ tcz/ none/combination)

Dose in mg/day:

Treatment started: ----------

Aspirin: y/n Statins: y/n Antihypertensive: y/n

Steroid started: y/n Steroid dose started: ----------

Immunosuppressant given: (choices can be aza/ cyclo/ mmf/ tcz/ none/combination)

Immunosuppressant dose: ----------

Intervention: y/n

Intervention : ----------

Activity at time of procedure: a/s/ g /na

Comments: ----------

Serial No.

Follow up visits: no. Date:

New symptoms: y New pulse loss: n New bruit: n

New symptom description: ----------

ITAS ESR in mm/hr CRP in mg/l:

ITAS A: Kerr score: PGO:

Patient global assessment:

TADS:

Angiographically: active (active/ inactive)

Angiographic extent: ----------

In stent Restenosis:

New areas of involvement: y (y/n)

Interventions: ----------

Other investigations: ----------

Current Steroid dose:

Current Immunosuppressant: none (choices can be aza/ cyclo/ mmf/ tcz/ combination/none)

Steroid dose given:

Immunosuppressant given: (choices can be aza/ cyclo/ mmf/ tcz/ none)

Dose of immunosuppressant:

Relapse: y/n

Persistently active disease: y/n

Stable disease: y/n

Annexure 2b: Patient Information Sheet

Study title: A study to determine the frequency of HLA-E variants and prognosis in patients with Takayasu Arteritis (TA).

Short title : HLA-E in Takayasu Arteritis

Takayasu arteritis is an autoimmune disease a characterized by inflammation and later on narrowing of large blood vessel. It manifests as symptoms of loss of blood supply to various organs of body. None of the prior research has been able to pinpoint the factors influencing susceptibility and outcome of patients with TA. In this study we plan to determine i) the association of HLA-E variants (HLA-E*01:01 and HLA-E*01:03) with disease susceptibility, phenotype and treatment response in our patients with TA, ii) the clinical profile and prognosis of TA patients. The study would be undertaken in department of Clinical Immunology and Rheumatology, CMC Vellore. Seventy five subjects with TA and 150 healthy controls would be recruited. The study participants would be interviewed about their personal and clinical details at baseline visit and follow up visit (till December 2014). 10ml blood would be withdrawn from patients and healthy controls only at the time of enrollment, after signing a written consent form (attached below). The blood sample would be processed for DNA extraction and HLA-E tying.

There are no risks or benefits to participants as a result of their participation in this study. The results of this study would be used for scientific publication purpose.

We, hereby, invite you to participate in this study as one of the subjects/ controls.

Investigator

Annexure 2c: Patient Consent Form

Subject Title: Study of HLA-E variants (HLA-E*01:01 i.e. ER and HLA-E*01:03 i.e. EG) in TA and its correlation with clinical parameters and outcome of disease

Short title : HLA-E in Takayasu Arteritis

Subject initials: _____ _____ _____ **Subject number: _____ _____ _____**

Age of Subject: _____ _____ _____

Please initial in the boxes if you agree

1. I confirm that I have read and understood the information sheet and have had the opportunity to ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or my legal rights being affected.	
3. I agree for my clinical details (excluding personally identifiable information) to be collected and recorded in a database.	
4. I agree for my personal information to be stored confidentially by the research team so that they can contact me in the future to invite me to participate in any future related research studies. I understand that my participation in any future related study will be entirely voluntary and I can decide not to participate.	
5. I understand that responsible members of the research team may look at sections of my medical notes where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
6. I understand that I may receive no direct benefit from participating in this study.	
7. I agree to the storage of my blood for use in future ethically approved studies.	
8. I understand that if I change my mind and withdraw consent from this study at a later date, any clinical information obtained until the time that I withdraw from the study will continue to be used for the study.	

Signature (or Thumb impression) of the Subject

…….

Date and time: _____/_____/_____ and _____:_____

DD / MM /YYYY

Full name……...

Name of Researcher……

Signed……

Date and time: _____/_____/_____ and _____:_____

DD / MM / YYYY

Name of Person Conducting Informed Consent Discussion: _____

Signature of the Witness:_____

Date and time:_____/_____/_____ and _____:_____

DD / MM /YYYY

Name of the Witness: _____

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

Date and time: _____/_____/_____ and _____:_____

Annexure 3: Baseline data sheet

sid	typ	date of 1st v	genotyp	sex	add	ageyr	ageon	deldia	dursy	comorbi	codm	cochd	cooldtb	coacttb	gen	angio		cori	pul	DCM	AR	compl	coro	rticar	lticar	rtcca	ltcca	rtscla	ltscla	rtver	ltvera	rtbra	ascad	arch	desth	abdao	coea	sma	ima	rtrena	ltrena	rtcia	ltcia	aneu	sten	occu	malai	fatig
1	1	16-11-2012	2	1	4	28	23	60	60	2	2	2	2	2	2	5	9	2	2	2		poor n	2	2	2	2	2	1	2	0	0	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	1	1
2	1	19-11-2012	1	2	2	32	29		36	2	2	2	2	2	1	5	13	2	2	2		2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	1	2	2	2	1	2	2	2	1	2	2	1
3	1	19-11-2012	2	2	4	48	46	24	24	1	2	2	2	2	2	4	13	2	2	2		creat r	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2	2	1	1	1	1
4	1	19-11-2012	2	1	3	31	15	120	120	2	2	2	2	2	2	2b	0	2	2	2	1	mild A	2	2	2	2	2	1	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	1	2	2
5	1	24-11-2012	2	2	2	33	18	17	204	2	2	2	2	2	2	5	3	2	2	2		2	2	2	2	1	2	1	2	2	2	2	2	1	2	2	2	2	1		2	2	2	1	2	2	2	2
6	1	13-12-2012	3	2	1	21	21	3	3	2	2	2	2	2	3	5	9	2	2	2		2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	1	1	2	2	2	1	1	1	1	1	1	1
7	1	17-12-2012	3	2	4	26	24	24	24	2	2	2	2	2	3	5	10	2	2	1	1	severe	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	1	2	2	2	2	2	1	1	1	1	1
8	1	11-12-2012	2	2	1	30	30	15	45	2	2	2	2	2	2	4	6	2	2	1	2	DCMY	2	2	2	2	2	2	2	2	2	2	2	1	1	2	1	2	1	2	2	2	2	1	2	2	2	1
9	1	02-10-2012	2	2	4	38	28	0	120	1	2	2	2	2	2	1	8	2	2	2	2	2	2	2	2	1	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2
10	1	22-11-2012	2	2	3	30	20	9	9	2	2	2	2	2	2	4	17	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	1	1	1	2	1	1	2	2
11	1	10-12-2012	3	1	2	51	50	60	60	2	2	2	2	2	3	5	7	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	2	2	2
12	1	19-12-2012	3	2	3	17	16	12	6	2	2	2	2	2	3	4	9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	1	1	2	2	2	1	1	1	2	2
13	1	17-12-2012	2	2	3	46	46	2	2	2	2	2	1	2	2	1	9	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2
14	1	27-12-2012	2	2	3	19	16	36	36	2	2	2	2	2	2	1	18	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2
16	1	04-01-2013	2	1	1	22	20	20	24	2	2	2	2	2	2	2a	9	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2
17	1	07-01-2013	2	2	2	46	40	11	72	1	2	2	2	2	2	2b	9	2	1	2	1	AR, C	2	2	2	2	2	0	1	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1
18	1	11-01-2013	3	2	2	20	14	72	73	2	2	2	2	2	3	5	9	2	2	1	1	dcmy	2	2	2	2	2	2	1	1	2	2	2	2	2	2	1	1	2	2	2	1	2	2	2	1	2	2
19	1	09-11-2012	1	2	1	26	21	24	60	2	2	2	2	2	1	5	23	2	2	2	1	AR	1	2	2	1	1	1	1	2	1	2	2	2	2	1	1	1	2	2	1	1	2	2	2	1	1	2	1
21	1	07-01-2013	3	2	2	17	14	12	32	2	2	2	2	2	3	5	7	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1	1	2	2
22	1	21-01-2013	2	2	3	11	9	15	17	2	2	2	1	2	2	5	24	2	2	1	2	DCMY	2	2	2	1	1	1	1	2	2	2	2	2	1	1	2	2	2	2	1	1	2	2	2	1	2	1	1
23	1	24-01-2013	3	2	2	15	14	6	6	2	2	2	2	2	3	2b	8	2	2	1	1	mi	DCMY	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	1	2	2
24	1	01-02-2013	1	2	3	17	16	6	6	2	2	2	2	2	1	4	9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	1	2	2	2	1	2	1	1
25	1	21-10-2012	2	2	4	16	14	20	24	2	2	1	2	2	2	5	10	1	2	2	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	1	1	2	2	2	1	2	2
26	1	14-02-2013	2	2	3	37	37	1	2	2	2	2	2	2	2	5	13	2	2	2	1	mi	2	2	1	2	2	1	1	2	2	2	1	2	2	1	1	1	2	2	1	1	1	1	2	1	1	2	2
27	1	19-02-2013	2	2	1	16		6	6	2	2	2	2	2	2		17			1	1	mi	CCF																							2			2	1
28	1	06-03-2013	1	2	1	19	18	6	9	2	2	2	1	2	1	5	6	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	2	2	2
29	1	07-03-2013	1	2	1	16	15	6	12	2	2	2	2	2	1	5	10	1	2	2	1	tri	CVA,	1	2	2	2	2	1	1	2	2	1	1	2	2	1	1	1	2	2	1	1	2	2	1	1	2	2
30	2	27-02-2013	3	2	1	60	58	1	18	2	2	2	2	2	3	5	0	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	2	2	2	2	2	1	1	2	2	2	1	1	2	2	2	2	2
31	1	07-03-2013	3	1	1	34	32	6	18	1	2	2	2	2	3	1	12	2	2	2	2	2																							2			2	2
32	2	11-03-2013	2	2	2	20	16	18	68	2	2	2	2	2	2	5	7	2	2	2	mild	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	1	1	2
33	1	14-03-2013	2	1	2	23	20	36	36	2	2	2	2	2	2	5	6	2	1	2	2	2	2	2	2	2	2	2	3	1	2	2	2	1	2	2	2	2	2	2	2	2	1	2	2	1	1	2	1
34	1	08-04-2013	1	2	4	54	41	65	65	1	2	1	2	2	1	4	6	1	2	1	2	DCMY	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	1	1	1
35	1	08-04-2013	1	2	1	29	24	60	60	2	2	2	2	2	1	5	9			2	1	AR	2																						2			1	1
37	1	15-05-2013	1	2	1	22	17	12	60	2	2	2	1	2	1	5	21	2	2	2	2	2	2	2	2	1	2	2	1	2	1	2	2	2	2	2	2	2	2	1	1	1	1	2	1	1	1	1	1
38	1	16-05-2013	3	2	1	31	31	0	6	2	2	2	2	2	3	5	9	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	1	2	2	2	2	1	2	2	1	1	2	1	1	2	1
39	1	09-04-2103	3	2	1	37	34	6	35	2	2	2	2	2	3	1	18	2	1	2	2	optic a	2	2	2	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	1
40	1	12-06-2013	2	2	1	36	34	18	18	2	2	2	2	2	2	5	3	2	2	2	2	HTn e	2	2	2	2	2	1	1	2	2	2	2	2	2	1	1	2	1	1	2	2	2	1	1	2	2	2
41	1	10-06-2013	1	2	1	23	19	40	48	2	2	2			1	3	15	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2
42	1	14-06-2013	1	2	4	26	20	70	70	2	2	2	2	2	1	5	22	2	2	2	2	RK sh	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	1	1	2	2	1	1	2	1	2	1
44	1	12-03-2013	2	2	1	29	28	21	24	2	2	2	2	2	2	1	13	2	2	2	2	2	2	2	2	2	1	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1
45	2	19-06-2013	2	2	1	30	30	0	6	2	2	2	2	2	2	5	16	2	2	1	2	accele	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	1	1	2	2	2	1	1	1	2
46	2	21-06-2013	1	1	4	33	33	4	4	1	2	2	2	2	1	4	12	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	1	1	1	2	2	2	2
47	1	27-06-2013	2	2	3	42	27	180	180	1	2	2	2	2	2	5	12	2	1	2	1	PAH, LK	shrunken																						2			1	2
48	1	08-07-2013	3	2	1	26	23	18	30	2	2	2	2	2	3	1	13	2	2	1	1	AR, D	2	2	2	2	2	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1
49	1	01-07-2013	3	1	4	28				1	2	2	2	2	3	5	5	1	2	2	2	2	1	2	2	2	2	1	1	2	2	2	1	2	2	2	2	2	2	1	1	1	2	2				
50	1	25-06-2013	1	2	1	27	27	5	5	1	2	1	2	2	1	1	9	1	2	2	2	2	2	1	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2
51	1	22-07-2013	2	2	1	18	18	4	5	2	2	2	1	2	2	5	11	2	1	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	2	2	2	1	1	2	2	1	2	2	2
52	1	12-04-2013	1	2	3	15	14	9	9	2	2	2	2	2	1	5	13	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1	1	1	1	2	1	1	2	1	2	1	1	2	1
53	1	15-07-2013	2	2	4	17	16	13	13	2	2	2	2	2	2	4	7	2	1	1	1	mi	dcmy	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	2	1	1	1	1	1
54	1	08-07-2013	1	2	4	26	19	84	84	1	2	2	2	2	1	1	14	2	2	2	2	2	2																						2	1		2	2
55	1	29-07-2013	1	2	2	16	13	30	30	2	2	2	2	2	2	1	5	22	2	2	1	2	sever l	2	2	2	2	1	1	1	2	2	2	1	2	1	1	1	2	2	2	2	2	2	2	1	1	1	1
56	1	30-07-2013	1	2	4	41	20	96	240	1	2	2	2	2	2	1	5	11			2	1	sever A	2	2	2	1	1	1	1	2	1	1	2	2	1	1	1	1	2	2	2	2	2	2				2	2
57	1	05-08-2013	1	2	4	17	17	7	7	2	2	2	2	2	2	1	3	10			2	2	2																						2			1	1
58	1	20-06-2013	2	2	1	28	24	6	48	2	2	2	2	2	2	4	19	2	2	1	2	sever l	2														1					1	1			2	1		2	2
59	1	04-09-2013	2	2	3	26	26	1	5	2	2	2	2	2	2	5	11	2	0	1	2	accele	2	2	1	2	2	2	1	2	2	2	2	2	1	2	2	2	2	1	1	2	2	2	1	1	2	1
60	1	09-08-2013	2	2	1	48	44	48	48	2	2	2	1	2	2	5	13	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2	2	1	1	1	2	2	2	2	2	2	2	1	1	2	2
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142	4	19-03-2012	3	2	1	31	30		5	2	2	2	2	2	3	1	7	2	2	2	2	stroke	2	2	2	1	1	1	2	1	2	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2
143	4	16-09-2013	2	2	1	33	32		19						2	4	4	2	2	2		2																	1	1		1	1			2				
144	4	27-01-2010	3	2	1	49	37	36	144	2	2	2	2	2	3	5	7	2	2	2	mod	2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	1	1	1	2	2	1	1	2	2	1	1	1	2	2
145	4	27-01-2010	2	1	1	11	10	6	13	2	2	2	2	2	2	4	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	1	2	2	2	2	1	1	2	2
146	4	11-09-2014	3	2	1	26	20	12	60	2	2	2	2	2	3	5	4	2	2	2	seve	2	2	2	1	1	1	1	1	2	2	1	1	1	1	2	2	2	2	2	2	2	1	2	2	1	1	2	2	2

147	4	27-06-2011	3	2	1	16	13	36	36	2	2	2	2	2	3	5	6	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	1	1	1	2	1	1	2	2	2	1	1	1	2
148	4	12-03-2012	3	2	1	34	26	72	95	2	2	2	2	2	3	5	8	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	1	1	2	2
149	4	03-10-2013	2	2	1	42	39	36	60	2	2	2	2	2	2	5	9	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	1	2	1	1	1	1	2	2	2	1	2	1	1	1	2	2
150	4	06-03-2012	2	2	1	27	25	3	12	2	2	2	2	2	2	1	12	2	2	2	2	2	2	2	2	1 (lat	1	2	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2
151	4	01-11-2012	2	2	1	24	19	0	32	2	2	2	2	2	2	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	1	2	2	2	1	2	2	2
152	4	01-08-2013	2	2	1	34	29	60	108	htn	2	2	2	2	2	1	8	2	2	2	mo	mod A	2	2	2	1 (lat	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2
153	4	17-02-2010	2	2	1	29			22	htn	2	2	2	2	2	1	8	2	2	2	2	nil	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1
154	4	29-06-2014	2	1	4	45	40	24	59		2	2	2	2	2	5	2	1	2	2	2	2	1	2	2	2	2	1	1	2	2	2	2	2	2	2	1	2	2	1	1	2	2	2	1	2	2	2
155	4	23-01-2012	2	2	1	48			11	2	2	2	2	2	2	4	2	1	2	2	2	CKD	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	1	2	2	2	1	1	2	2
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157	4	09-09-2011	2	1	3	42	42	2	44	2	2	2	2	2	2	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	1	1	2	2	2	1	2	2	2
158	4	12-02-2014	2	1	4	50	40	60	110	2	2	2	2	2	2	5	6	1	1	2	2	CVA 2	1	2	2	1	1	1	1	2	2	2	2	2	1	1	2	2	2	1	1	2	2	2	1	2	2	2
159	4	13-10-2014	1	2	1	40	28	60	120	2	2	2	2	2	1	5	6	2	2	2	2	2	2	2	2	2	1	1	2	2	1	2	2	2	1	1	2	2	2	2	2	2	2	2	1	2	2	2
160	4		3	1	3	26	26	3	3	2	2	2	2	2	3	1	4	2	2	2	2	CVA	2	2	1	2	2	2	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2
161	4	05-09-2013	3	1	1	33	24	0	96	2	2	2	1	2	3	4	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	2	1	2	2	2
sid	type	dt	genotyp	sex	add	ageyr	ageon	deldiag	dursy	comorbi	codm	cochd	cooldtb	coacttb	gen	angio	deitak	cori	pul	DCM	AR	compl	coro	rticar	lticar	rtcca	ltcca	rtscla	ltscla	rtver	ltvera	rtbra	ascad	arch	desth	abdad	coea	sma	ima	rtren	ltren	rtcia	ltcia	aneu	sten	occu	malai	fatig

wtloss	fever	gan	muc	claud	visua	pervis	headac	syncol	cva	card	abd	dysp	chesp	syshf	raicrea	carotid	abspul	bruit	itas	esr90	crp	itasa	kersc	pgo	tads	prio	pristat	priantih	psteroid	pimmun	immu	aspirin	statins	antihtn	sterst	sterdo	immng	immn	inter	diseas	echo	imagi	actpr
1	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	6	29	5.17	6	3	1	6	2	2	1	0	7	0	1	2	1	1	25	3	2000	2		normal	TA(ot	4
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2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	1	2	1	2	14	43	1.18	14	2	1	8	2	2	1	0	7	0	1	1	2	1	30	1	3	2	stable i	mild M	nil, ot	4
2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	0	3	0.96	0	0	2	5	1	1	1	7.5	1	100	1	1	2	1	7.5	1	100	1		normal		2
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2	1	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	1	12	74	5	12	4	1	2	2	2	1	0	7	0	1	2	1	1	40	3	2000	1		NORM	0	1
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1	2	2	2	1	2	2	2	2	2	1	2	1	2	1	2	2	2	2	9	98	10.4	13	4	1	3	2	2	1	0	7	0	1	2	1	1	40	3	2000	1	minor i	lvh mil	CTan	1
2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	1	11	32	13	13	4	3	8	1	2	2	2	7	0	1	1	2	1	22.5	3	1440	1	only m	normal	BIH i	3
2	2	2	2	1	2	2	2	2	2	2	2	1	2	1	2	2	1	2	0	30	0.5	0	0	2	17	1	2	1	25	3	2000	1	2	1	1	25	3	2000	2	stable i	NIL	NIL	4
2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2	0	8	0.9	0	0	2	5	1	1	1	5	3	1080	1	1	1	2	5	3	1080	2	stable	nil	nil	2
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2	1	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	1	1	0	15	0.1	0	0	2	3	1	1	1	5	3	2000	1	1	1	1	4.5	3	1750	2	ltfup	normal	LCCA	4
2	2	2	2	1	1	2	1	1	2	2	2	2	2	2	1	2	2	2	1	1	0	5	5.82	0	3	2	16	1	1	1	25	1	2000	1	1	1	1	22.5	3	2000	1	monop	NORM	NIL	2
2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	1	1	2	12	30		13	1	1	2	2	2	2	0	6	15	2	2	2	1	25	3	1000	2	active i	myxom	PETC	4
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	5	120	44.8	11	2	1	13	2	2	2	2.5	6	7.5	1	2	1	1	37.5	5	1440		persita	mod AI	FDG	4
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2	1	2	2	1	2	2	1	2	2	2	2	1	2	1	2	2	1	1	18	14	3.44	14	1	3	14	2	2	2	10	7	0	1	2	1	1	35	3	1000	1	relaps	Hypert	MRA	3
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0	12	16.6	2	2	3	11	1	2	2	12.5	4	8	1	2	2	1	12.5	3	2000	1	relpase	normal	nil	3
2	1	2	2	1	2	2	2	2	2	1	1	1	2	2	1	1	1	1	0	2	0.16	0	0	2	14	1	2	1	10	5	2000	1	2	1	1	7.5	5	2000	2	in rem		lipids	4
2	1	2	2	2	2	2	1	2	2	1	2	1	2	2	2	2	1	2	2	11	0.72	2	0	2	5	1	2	2	40	3	2000	1	2	2	1	10	3	2000	1	angio r	MOD L	NIL	2
1	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	1	12	44	21.3	17	2	1	1	2	2	2	0	7	0	1	2	2	1	20	3	2000	1	relapsi	NIL	RENA	1
2	2	2	2	1	2	2	2	2	2	1	1	1	1	2	2	2	2	1	13	34	5.52	13	3	1	7	2	2	2	0	7	0	1	2	1	1	20	3	1440	1	only ar	Concer		1
2	2	2	2	1	2	2	1	2	2	2	2	1	2	1	2	2	2	1	15	57	5.1	59	3	1	10	2	2	1	40	2	0	1	2	1	1	45	3	2000	1	persista	Concer	Ct ans	1
2	2	2	2	2	2	2	2	2	2	1	2	1	2	1	2	2	1	1	20	15	14.7	22	3	1	10	2	2	1	0	7	0	2	2	1	1	20	3	2000	2		sevee L	not de	4
2	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	1	2	3	5	0.15	3	0	3	4	2	2	2	15	3	1000	1	2	2	1	20	3	2000	1	probab	nil	outsid	2
2	2	2	2	2	1	2	2	2	1	2	2	2	2	1	2	2	2	1	0	8	2.15	0	0	2	9	1	2	1	10	6	25	1	2	1	1	25	3	2000	1	persista	trvial A	CT la	2
2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0	14		0	0	2	5	1	2	1	25	1	125	1	2	1	1	22.5	1	125	2	persista	NORM	NIL	2
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2	1	2	2	1	2	2	2	2	2	2	2	2	1	1	2	2	1	1	6	89	21	9	3	1	22	1	1	1	12.5	3	2000	1	2	1	1	20	3	2000	2	persista	mild A	norma	4
2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	1	8	70	13.7	13	3	1	6	2	2	1	0	7	0	1	2	1	1	35	3	2000	1	ltfup	normal	outsid	1
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2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	8	73	54.2		2	3	2	2	2	2	5	1	100	1	2	2	1	35	3	2000	2	relapse	AR WI	PETC	4
2	1	2	2	1	2	2	1	2	2	2	2	1	1	1	2	2	1	2	3	30	8.7	5	3	3	16	2	2	1	40	6	15	1		1	1	37.5	5	2000	1	progres	normal	tight s	3
1	2	2	2	1	2	2	2	2	2	2	2	2	1	2	2	2	1	1	14	33	6.29	15	4	1	9	1	2	2	0	7	0	1	2	2	1	30	3	2000	1	ltfup	2	nil	1
2	2	2	2	2	1	1	2	2	2	2	2	2	1	2	2	2	1	1	1	11	17	1.84	11	4	3	13	1	2	2		3	2000	1	2	2	1	50	3	2000	1	persista	normal	eye :	3
2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	1	67	12.7	6	0	1	5	2	2	1	0	7	0	1	1	1	1	50	3	1000	1	relapsi	normal	CT ar	1
2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	2	2	1	2	0	32	17	2	3	3	11	2	2	2	0	7	0	1	2	1	1	25	3	2000	1	persista	normal	outsid	3
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2	1	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	1	1	0	7	2.46	0	0	2	11	2	2	2	10	6	10	1	2	2	1	30	3	2000	1	relapse	normal	CT ar	2
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1	1	2	2	1	2	2	1	2	2	2	1	2	2	1	2	2	1	2	0	26	1.03	0	0	2	5	1	2	1	27.5	3	2000	1	2	1	1	25	3	2000	2	NON I	NORM	NIL	3
2	1	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	1		44	32.4			3	6	2	2	2	0	7	0	2	2	2	1		5	2000	2	NON I	PAH T	CT D	4
2	2	2	2	2	2	2	2	2	2	1	2	1	1	2	2	2	1	1	14	50	11.1	16	3	1	7	2	2	2	0	7	0	1	2	2	1	40	3	2000	2	PERSI	ef 18%	ct ang	4
2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1	7	1	0.41	7	1	2	6	2	2	2	0	7	0	1	1	2	2	0	7	0	2	stable I	Concer		4
1	2	2	2	1	2	2	2	2	2	1	2	1	1	2	2	2	1	2	10	105	75.4	16	4	1	3	1	1	2	0	7	0	1	2	2	1	40	3	2000	2	LTFUI	mild Lv		4
2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	12	15	1.43	12	2	3	10	2	2	1	0	7	0	1	1	2	1	27.5	3	2000	1	persista	normal	LUL (	3
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	14	44	4.43	15	2	1	6	2	2	1	0	7	0	1	2	2	1	22.5	3	2000	2	PROG	normal	nil	
1	2	2	2	2	2	2	2	2	2	1	2	1	1	1	1	2	2	1	8	76	25.7		2	1	6	2	2	1	0	7	0	1	2	1	1	35	6	15	2	PERSI	EF 39.3	renal	4
2	1	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	1	1	18	35	10.2		3	1		2	2	2	0	7	0	1	2	1	1	15	1	50	2	LTFUI		dople	4
1	2	2	2	1	2	2	2	2	2	2	1	2	1	2	2	2	2	1	1	24	65	15	28	3	1	11	2	2	2	0	7	0	1	1	1	1	30	3	2000	1	STABI	severe	LA/A	1
2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	1	2	2	2	1	12	45	17.1	4	2	1	6	1	2	1	0	7	0	1	2	1	1	30	5	2000	1	STABI	mod AI	MRA	3
2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	1	11	6	0.15	11	1		5	2	2	1	0	7	0	2	2	1	1	20	3	2000	2		conc L	doppl	4
2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2	1	2	0	8	18.2	3	2	2	17	1	2	1	0	1	75	1	2	1	1	35	3	1080	2	LOST	LV yst	lst ans	4
1	1	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	1	1	0	28	7.9	1	2	3	10	2	2	1	10	2	0				1	10	3	2000		LOST	mild A	outsid	0
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	17	48	28	20	4	1	8	2	2	2	0	7	0	1	2	2	1	37.5	6	15	2	Clin re	normal	angio	4
1	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	1	1	8	55	7.9	9	2	3	3	2	2	2	0	7	50	1	2	1	1	50	3	2000	2		normal	Atrial	4
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2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	80	3.47		1	1	1	2	2	1	0	7	0	1	2	1	1	22.5	3	2000	1	ACTIV	normal	mr an	1
2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	1	0	17	2	0	0	2	3	1	1	1	0	7	0	1	1	1	1	30	6	15	2	PERIS	AR mil	2009	4
2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	4	38	12.7	6	3	1	4	2	2	1	0	7	0	1	2	1	1	50	6	12.5	2		ND	MR a	4
1	1	2	2	1	2	2	1	1	2	2	2	2	2	2	2	1	2	1	4	45	12.5		2	1	3	2	2	2	1	6		1	2	2	1	40	3	2000	2	persista	trileafle	outsid	4
2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	1	0	10	0.17		0	3	10	1	2	2	0	7	0	1	2	1	1	20	6	15	1	GRUM	normal	angio	4
1	2	2	2	1	2	2	2	2	2	1	1	1	2	2	2	2	2	6	18	12.8	8	2	1	3	2	2	2	2	0	7	0	1	2	2	1	20	3	1080	2	PERSI	severe	angio	4
2	2	2	2	1	2	2	2	2	2	2	1	2	2	1	1	2	2		7	25	3.4	7	1	3	5	2	2	1	40	6	10	1	2	1	1	20	3	2000	1	ACTIV	normal	outsid	3
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	60	70.3	5	1	1	2	2	2	2				1	2	1					LOST	no hyp		
1	1	2	2	1	2	2	1	1	1	2	2	2	2	2	2	2	1	1	26	92	15.5	28	4	1	8					7	0	1	2	2	1	35	3	2000	2	LOST	normal	lt fron	4

2	1	2	2	1	2	2	1	1	2	2	2	1	2	1	2	2	1	1	23	40	11.2	25	3	1	17	2	2	1	0	7	0	1	2	1	1	50	6	15	2	ONLY	trace M	nil	1
2	2	2	2	1	2	2	1	2	2	1	2	2	1	1	2	2	1	2	11	26	13.9	3	3	3	12	1	1	1	0	7	0	1	1	1	1	10	3	2000	1	LOST	normal	CTA	3
2	2	2	2	2	2	2	1	2	2	2	1	2	2	1	2	2	2	2	5	24	50.3		4	1	3	2	2	1	60	6	15	1	2	1	1	35	3	2000	1	stable	normal	MRA	1
2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	4	9	3.4	4	2	2	6	2	2	2	0	7	0	1	1	2	1	25	6	15	1	CLINI	normal	nil	4
2	1	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	8	12	7.87	9	3	1	0	2	2	2	0	7	60	1	2	1	1	60	3	1080	2	CLINI	ND	CTA:	4
2	1	2	2	1	1	2	2	2	2	2	2	2	2	1	2	2	1	1	19	5	6.2	19	3	3	11	2	2	2	40	7	0	1	2	1	1		3	2000	2	CVA c	LVH ,	doppl	4
2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	3	33	35.8	6	2	1	9	2	2	2	17.5	3	1000	1	1	2	1	45	3	2000	1	angio r	LVH +		1
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	6	16	2.19	6	1	3	1	1	2	2	20	7	0	1	2	2	1	20	3	2000	2	CLINI		CTA	4
2	1	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	1	1	12	42	17.9	15	3	1	11	2	2	1	0	7	0	1	1	1	1	50	3	2000	1	DELA	LV sys	LIPID	1
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	1	2	1	1	0	86	14.8	2	2	3	10	2	2	1	0	1	75	1	2	1	1	30	3	2000	1	stable	normal	MRA	1
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	3	50	3.1	3	1	2	6	1	1	1	0	7	0	1	2	2	1	30	3	2000	1	LOST	noemal	nil no	2
2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	2	2	1	11	79	38.4	14	3	1	1	2	2	2	7.5	7	0	2	2	2	1	50	3	2000	1	LOST	normal	CTAI	1
2	1	2	2	1	1	2	2	2	2	2	2	2	1	2	2	2	2	1	1	34	23	4	2	1	6	2	2	2	10	4	720	1	2	1	1	27.5	3	1440	1	PERSI	AR mil	dec20	1
2	2	2	2	2	2	2	2	2	2	1	2	1	1	2	2	2	2	1	7	29	15	9	3	1	1	2	2	2	0	7	0	1	1	1	1	30	3	1440	2	STABI	normal	nil, li	4
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	1	0.17	0	1	2	0	2	2	2	80	7	0	2	2	2	1	75	3	2000	2	CARD	an infi	PET :	4
2	2	2	2	1	2	2	1	1	2	2	1	2	2	1	2	2	1	1	4	17	5.9	4	1	3	7	1	2	1	0	7	0	1	2	1	1	25	3	1440	1	STABI	normal	outsid	3
2	2	2	2	1	1	2	2	2	2	2	1	1	2	1	2	2	1	1	17	33	8.38	18	3	3	10	2	2	1	2	7	0	1	2	1	1	30	3	2000	1	LOST	LVH re	nil	
2	2	2	2	1	2	2	2	2	2	1	1	2	1	2	2	2	2	1	0	25	17.9	0	1	2	13	1	1	1	7.5	1	100	1	1	1	2	5	1	100	2	MINO	Basal s	Ct s/o	2
2	2	2	2	1	2	2	2	1	2	2	2	2	2	1	2	2	1	2		85	19		4	1	9			1	0	7	0	1	2	1	1	30	3	2000	1	relapsi	mild A	nil	1
2	2	2	2	1	2	2	2	2	2	1	2	1	2	1	2	2	1	2	8	35	5	8	2	1	12	1	1	1	0	7	0	1	2	2	1	60	3	2000	1	flare w	oct 201	left ki	1
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	2	1	0	14	6	0	0	2	3	2	2	1	1.25	3	2000	1	2	1	1	1	3	2000	2	monop		nil	2
2	2	2	2	1	1	2	1	1	2	2	2	1	2	2	2	2	1	1	0	51	31.1	3	1	2	12				0	7	0	1	2	1	1	50	3	2000	1	monop	LVH w	outsid	2
2	2	2	2	2	2	2	2	2	2	1	2	1	2	1	2	2	1	1	12	50	27.4	15	3	1	6	2	2	1	0	7	0	2	2	1	1	30	3	2000	1	too ear	lvf, htn	left ki	1
2	1	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	37	14	4	1	3	7	1	2	1	0	7	0	1	2	1	2	0	7		1	ltfup	globalL	2	
2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	3	38	18.6	6	2	3	5	1	2	1	12.5	3	2000	1	2	1	1					Isr of c	AR -po	nil	3
2	2	2	2	1	2	2	2	2	2	2	2	1	1	2	2	2	1	2	0	10	0.2	0	0	2	4	2	2	2	0	7	0	1	2	2	1	25	3	2000	1	stable	normal	egc -	2
2	2	2	2	1	1	2	2	2	2	1	2	2	1	1	2	2	1	2	0	53	5.8	0	0	2	5	1	1	1	15	6	25	1	1	1	1	15	5	480	1	progres	normal		1
2	2	2	2	1	1	2	1	1	2	1	2	1	1	1	2	2	2	1	11	70	18.2	14	4	1	5	2	2	1	0	7	0	1	1	1	1	20	6	15	2	relapse	NORM	CAD	4
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	0	25	34.5	3	1	3	8	1	2	1	7.5	3	2160	1	1	1	1	7.5	5	2160	1	progres	grade 1	HRCt	3
1	1	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2	1	1	18	44	49.1	21	4	1	8	2	2	2	0	7	0	2	2	2	1	22.5	3	1040	2	LOST	normal	homo	4
2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	1	0	34	4.61	0	1	3	6	1	2	2	5	7		1	2	2	1	20	1,3,5,3		1	progres	LVdysf	LRA	1
1	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	23	37	11.1	25	3	1	12	2	2	2	10	6	7.5	1	2	2	1	35	3	2000	2	stable	normal	CTA	1
2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	1	2	2	2	4	3	3.25	4	1	2	3	2	2	2	0	7	0	1	2	1	1	10	3	2000	1	angio p	normal		2
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	5	59	7.26	6	2	1	0	2	2	2	0	3	25	1	2	2	1	25	3	2000	2	short f	nl	doppl	4
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	8	79	11.6	10	2	1	5	2	2	2	0	7	0	1	2	2	1	12.5	7	0	2	lost to	normal	only c	4
2	1	2	2	1	2	2	2	2	2	1	2	1	1	2	2	2	1	1	1	39	67.8	4	1	1	7	2	2	2	15	6	15	1	1	2	1	30	6	20	2	no fup	outside	cMRI	4
2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	0	42	4.45	0	2	2	5	2	2	1	0	7	0	1	2	1	1	10	3	2000	2	stable	normal	Right	4
1	1	2	2	1	2	2	2	2	2	1	2	1	1	2	2	2	1	1	21	68	85.1	24	3	1	14	1	1	1	5	1	100	1	1	1	1	60	3	2000	2	aggres	LVH, n	mri :a	4
1	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	5	20	11.4		3	1	4	2	2	2	0	7	0	1	2	1	1	30	3	2000	1	stable	normal	nil	1
2	2	2	2	1	2	2	2	2	2	1	2	1	1	1	2	2	1	1	26	84	55.1		4	1	13	2	2	1	0	7										stable	MODE	RENA	0
1	2	2	2	1	1	2	1	2	2	2	2	1	2	2	2	2	1	2	11	47	64.7		3	1	5	2	2	2	10	7	0	1	2	2	1	45	3	2000	1	stable	mild A	nil, la	1
1	1	2	2	1	2	2	1	2	2	2	2	1	2	1	2	2	1	1	3	15	1.05		2	3	11	2	2	1	10	6	10	1	2	1	1	20	3	2000	2		TR mil	PWC	4
2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	1	1	0	10	2	0	0	2	10	2	2	1	10	6	10	1	2	1	1	20	3	2000	2				4
2	2	2	2	2	2	2	2	2	2	1	2	1	1	2	2	2	1	1	13	41	3		3	1	5	1	2	1	0	7	0	1	2	1	1	15	5	2000	1	persist	LVH	HRC	1
2	1	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	6	16.7		2	2	3	2	2	2	0	7	0	1	1	2	1	25	3	2000	1	stable	normal	norma	2
1	1	2	2	1	2	2	1	2		1	2	1	2	2	2	2	1	1	20	81	21.4		3	1	12	2	2	2	0	7	0	1	2	1	1	40	6	15	2	no fup,	EF 21,	homo	4
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	4	44	87.5		2	3	2	1	2	1	7.5	3	2000	1	2	1	1	25	5	2000	1	past pr	sever A	PETC	3
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	2	2	3	59	8.57		2	1	1	2	2	1	0	7	0	2	2	2	1	25	3	2000	2	no fup	not don	CT an	4
1	1	2	2	1	1		1	2	2	2	2	2	2	2	2	2	1	1	5	40	2.5		2	3	10	2	2	2	0	7	0	1	1	2	1	50	6	15	2	non pr	normal	VEP	4
2	2	2	2	1	2	2	1	2	2	2	2	2	2	1	2	2	2	1	7	42	13.6		3	1	2	2	2	1	0	7	0	1	2	1	1	30	3	2000	2	doing	normal	nil	4
1	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	3	13	4.11	3	3	1	9	2	2	2	0	7	0	1	1	2	no fup	0							
2	2	2	2	1	2	2	2	1	2	2	2	2	2	1	2	2	1	2	0	41	64.5	3	2	1	7	2	2	1	0	3	1440	2	1	1	1mg/kg	50	3	1440	2				4
2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2	2	0	22	0.7	0	0	1	1	1	2	1	1	1	2000	1	2	1	1mg/kg	35	3	2000	prev	progressive dse, RBA			1
2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	10	12	2.3	10	3		3				2	2	0	1	2	1	0.4mg/k	20	3	2000	2	still hypertensive, ES			4
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	2	1	7	45	2.3	7			3				2	2	0	1	2	1		35	2	50	2	stable dse			4
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	0	norma	norma	0			14	1	2	2	1	5	5 dose	1	2	2	1mg/kg	35	3	2000	1	repeated ISR, relapsi			1
2	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	2	1	1	3	29	17	5	2	3	1	1	2	2	1	3	2000	1	2	2	1mg/kg	35	3	2000	1	rptd isr with lab mild			3
2	2	2	2	1	1	2	1	2	2	2	2	2	2	2	2	1	1	1	2		20	4	2	1	10	1	2	2	1	3	2000	1	2	2	0.5mg/k	20	3	2000	1	persistant active dise			1
2	2	2	2	1	2	2	2	2	2	1	2	2	2	1	2	2	2	1		22	34.5			1	6	1	2	1	1	3	2000	1	2	1	1mg/kg	40	3	2000	1	persistant active dise			1
2	2	2	2	1	2	2	2	1	2	mild a	2	2	2	1	bilateral ras					16	4.92				5										0.5	7.5				monophasic			
2	2	2	2	1	2	2	1	1	2	2	2	2	2	1	1					6	0.3				0										0.25	10				relapse 5 months pos			0
2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	14	15	51	17	4	1	8	1	2	2	7.5	3	3000	1	2	2	1mg/kg	7.5	3	3000	1	cli stble, lab persistar			1
2	1	2	2	1	2	2	2	2	2	CHF	2	1	2	2	2	2	1	1	0	13	37	3	0	1	13	1	2	2	15	2-->3	2000	1	2	2	1mg/kg	15	3	2000	1	peristant CRp, Angio			3
2	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	1	2		4	13			1	6	1	1	1	50	3	2000	1	1	1	1mg/kg	55	3	2000	1	nonprogressive, poss			1
	2			2					2	lvh				1	1					59	47				3										0.5	30				persistent stable			
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	1	0	0	0	0	2	2	9	1	1	1		2--> 3	2000	1	2	1	0.5mg/k	20	3	2000	1	mild progression ,ISI			2
2	2	2	2	2	2	2	1	2	2	2	1	2	2	1	2	2	2	2	1		4.54	0	0	3	3	1	2	1	10	3	1000	1	2	1	1m/kg	20	3	1000	1	rptd diffuse ISRs, c/c			1
2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	hih	hih	4	2	1	2	1	2	2	7.5	2-->3	2000	1	2	2	0.5mg/k	20	2	75	2	persistant activity			

2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	0	58	3.75	0	1	2	5	2	2	2	0	7		1	2	1	1mg/kg	50	3	2000	2				
2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	2	2	1	2	4	35	8.7	5	2	3	4	1	2	1	35	3	2000	1	2	1	0.5mg/k	35	3	2000	1	rptd ISR RSCA ,LRA			2
2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	1	1	0	norma	normal				7	1	2	2	12.5	6	22.5	1	2	2	0.5mg/kg					nd			
2	2	2	2	1	1	2	2	2	2	2	2	1	1	2	2	2	1	1	0	26	26.7	3	1	2	9	1	2	1	30	3	2000	1	2	1	1mg/kg	30	3	2000	1	LCCA, LSCa stent rp			1
2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	0	18	0.9	0	0	2	0	1	2	2	5	3	2000	2	2	2	only 5 r	5	3	2000	1	mnophasic stable sca			2
2	2	2	2	1	2	2	1	2	2	mod A	2	2	2	2	2	2	1	1	3	41	13.6	2	2	1	8	1	2	1	1	1	2000	1	2	1	0.5mg/k	30	2	2000	1	angio new inv RCCA			2
2	2	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	1	2	0	20	7.5	1	1	2	7	1	2	1	1	3	2000	1	2	1	0.5mg/k	30	3	2000	1	angio ISR beyond ste			2
2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	0	4	1.04	0	0	2	3	1	1	1	5	3	1500	1	1	1	0.5mg/k	5	3	1500	1	angio new CAD at 9			2
2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	0						2	2	2	1	0	7		1	2	1	5mg/kg	5	3	2000	1	Minor Ra focal ISR,			2
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0	0	0	0	0	2	4	1	1	2	5	3	2000	1	1	2	1mg/kg	37.5	1	2000	1	stable monophasic			2
2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	0	0	0	0	0	1	4	1	1	1	1	3	2250	1	1	1	<0.25m	10	3	2250	1	stable monophasic			2
2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	2	1	0	0	0	0	0	1	8	1	1	1	1	3	2000	1	1	1	0.5mg/k	2.5	3	2000	1	angio new lesion			2
2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	1	0	13	0.4	0	0	1	2	1	2	1	1	1	100	1	2	1	1MG/K	40	3	100	2	stable monophaisc,th			0
2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	1	6	20	1.5	6	2	1	1	1	2	2	0	7	0	1			nil								
2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	0	0	0	0	0	1	3	1	2	1	5	2->3	2000	1	2		1mg/kg	40	2	2000	1	stable monophasic			2
wtloss	fev	ganva	muc	claud	visua	pervis	headac	synco	cva	card	abdpa	dysp	chesp	sysht	raicreat	carotid	abspul	bruit	itas at	esr90	crp	itasa	kersc	pgo	tads	prioa	pristat	priantih	psteroi	pimmun	immudo	aspirin	statins	antihtn	sterst	sterdo	immng	immnd	inter	disease	echo	image	0

Annexure 3: follow up data sheet

sid	dt	activity status	esr90	crp	itas	itasaCRP	itasAESR	fangio	intyes	immngiv	sterdogiven	Status	Angio progressi	angio progressio	compliance	fupdur
1	16-11-2012	1.00	29	5.17	6	7		0	nil	3	25.0	0	0			
2	19-11-2012	1.00	74	9.7	13	17			PTA with st of s	3	30.0	1	2		visit 5 defaulted	25
2	19-02-2013	0.00	23	0.3	0	0	0		not done							
2	16-05-2013	0.00	20	2	0	0	0	2	tads same as last	3	25.0					
2	23-12-2013	0.00	8	0.4	0	0	0		not done, b/l CB	3	10.0					
2	05-12-2014	0.00	23	0.4	0	0	0		not done	6	0.0					
3	19-11-2012	1.00	43	1.18	14	15			nil ? Done	1	30.0	1	2	not done	visit 1 defaulted	23
3	14-02-2013	0.00	32	3.2	0	0	1			3	27.5					
3	17-06-2013	0.00	21	0.9	0	0	0		not done	3	17.5					
3	24-11-2014	0.00	12	0.5	0	0	0	2	not done , color	3	4.0					
4	19-11-2012	0.00	3	0.955	0	0			POBA TO DTA	1	7.5	0	0			
5	24-11-2012	1.00	27	1.03	4	5			AO REPAIR W	3	50.0	1	2	APNP at 6 and	visit 1 defaulted	19
5	23-12-2013	0.00	59	2.3	0	0	2	2	LCCA,aortic, RI	3	30.0					
5	17-03-2014	0.00	25	0.5	0	0	1	2	all stents patent	3	20.0					
5	28-06-2014	0.00	30	0.4	0	0	1		nd ,but CT abd p	3	12.0					
6	13-12-2012	1.00	74	5	12	16			RRA RECAN&	3	40.0	0	0			0
7	17-12-2012	1.00	82	11.8	11	15			recan & stent to	3	30.0	0	0	nd		3
7	14-03-2013	0.00	19	10.5	0	1		2	nil	3	27.5					
8	11-12-2012	1.00	98	10.4	9	13			POBA RRA,PO	3	40.0	1	1	RRA 50% ISR, s	good	19
8	07-03-2013	0.00	52	4.5	0	0	2		not done	3	27.5					
8	06-06-2013	0.00	9	5.2	0	0	0	2	RRA 60%, LRA	3	20.0					
8	05-09-2013	0.00	10	4.1	0	0	0		not done	3	10.0					
8	16-12-2013	0.00	6	3.4	0	0	0	2	RRA ostial sten	3	4.5					
8	27-02-2014	0.00	18	4.6	0	0	0		not done	3	2.5					
8	25-07-2014	0.00	29	10.4	0	1	1	1	ist 50% RRA, at	3	10.0					
9	02-10-2012	1.00	32	13	11	13			PTA& st to RSC	3	22.5	2	2	minor ISR at las	good	21
9	03-01-2013	0.00	31	1.3	0	0	1	2	not done	3	20.0					
9	08-04-2013	0.00	12	2.4	0	0	0	2	SAME AS BEFO	3	12.5					
9	29-07-2013	0.00	8	0.1	1	1	0		not done	3	7.5					
9	08-01-2014	1.00	32	4.5	2	2	3	2	mild isr of LSCA	3	10.0					
9	24-07-2014	1.00	32	7.1	0	1	1	2	lsca <30%, rva r	3	5.0					
10	22-11-2012	0.00	30	0.5	0	0			NIL done earile	3	25.0	1	2	APNP at last ang	good	10
10	28-02-2013	0.00	46	0.4	0	0	1	2	all stents done pa	3	15.0					
10	12-09-2013	0.00	29	1.6	0	0	1		not done	3	5.0					
11	10-12-2012	0.00	8	0.9	0	0			PTA with stentir	3	5.0	1	2	nd		57
11	02-04-2013	0.00	9	1	0	0			not done dopler	3	3.0					
12	19-12-2012	0.00	21	0.5	0	0			not done due to	1	35.0	0	0			0
13	17-12-2012	0.00	15	0.1	0	0				3	4.5	0	0	nd		5
13	13-06-2013	0.00	52	0.4	0	0	2		not done	3	2.5					
14	27-12-2012	0.00	5	5.82	0	0			PTA WITH ST	3	22.5	1	2	nd	good	18
14	16-06-2014	0.00	23	2.3	0	0	0		not done	3	2.5					
16	04-01-2013	1.00	30		12	13			nil	3	25.0	2	0	nd		2
16	05-03-2013	1.00	26	32.5	2	5	3		not done	3	60.0					
17	07-01-2013	1.00	120	44.8	5	11			nil, ITAS now is	5	37.5	2	1	LSCA, RSCa IS	good	19
17	28-03-2013	1.00	44	48.1	0	3	2	2	Lsca, RSCA	3	35.0					
17	20-07-2013	1.00	42	28.8	3	6	5		not done	5	20.0					
17	15-10-2013	1.00	32	18	14	16	15		ISR 80% of RT	5	25.0					
17	16-07-2014	1.00	50	21.1	5	8	7		no new areas ISI	5	17.0					
18	11-01-2013	1.00	16	0.447	11	11			PTA st of rra, ls	3	30.0	1	1	ISR LSCA at 12	good	23
18	09-05-2013	0.00	13	0.1	0	0	0		not done	3	20.0					
18	03-08-2013	0.00	15	0.1	0	0	0		not done	3	12.5					
18	04-12-2013	0.00	5	0.2	3	3	3	1	ISR, no new ves	3	9.7					
18	22-11-2014	0.00	4	0.2	0	0	0		not done	3	6.5					
19	09-11-2012	1.00	14	3.44	18	14			LSCA recan goo	3	35.0	2	2	at 6 mo imld lsr	good	23
19	17-01-2013	0.00	30	9.8	0	1	1	2	no ISR ,lesions s	3	32.5					
19	11-04-2013	1.00	50	16.5	3	5	5		not done	3						
19	30-09-2013	1.00	54		0	0	2		not done	3	15.0					
19	09-12-2013	1.00	32	43.2	0	3	1		not done	3	10.0					
19	04-03-2014	1.00	49	6.4	4	5	6	1	Inm,RCCA, RS	3	15.0					
19	02-06-2014	1.00	49	10.1	2	3	4		not done	3	15.0					
19	18-07-2014	1.00	55	30.7	0	3	2	2	no ISR ,no new	3	20.0					
19	20-10-2014	1.00		20.8	0	3			not done	3	9.0					
21	07-01-2013	1.00	12	16.6	0	2			RSCA failed rec	3	12.5	2	1	new aenurysm,	good	18
21	08-01-2014	1.00	65	17.2	8	10	11	1	aorta aneurysm new, rest same as before							
21	14-07-2014	0.00	18	9.8	0	1	0		not done	3	7.5					
22	21-01-2013	0.00	2	0.159	0	0			nil now	5	7.5	1	0	nd	good	24
22	12-12-2014	0.00	23	1.3	0	0	0		not done	3	7.5					
23	24-01-2013	0.00	11	0.72	2	2			DTA PTA ST 2	3	10.0	1	1	both DTA,RSCa	good	6
23	18-07-2013	0.00	7	0.3	3	3		1	right SCA porx	3	10.0					
24	01-02-2013	1.00	44	21.3	12	17			RRA PTA WITI	3	20.0		0	not done	good	17
24	02-05-2013	0.00	17	0.6	0	0	0		not done	3	17.5					
24	29-07-2013	1.00	27	1.8	7	7	8		not done	3	25.0					
24	27-04-2014	0.00	42	4.1	3	3	5		not done	3	15.0					
24	28-07-2014	0.00	52	6.9	0	2	2		not done	3	12.5					
24	28-10-2103	1.00	43	3.8	8	8	9		not done	3	20.0					
25	21-10-2012	1.00	34	5.52	13	13			LCMA RECAN	3	20.0	1	1	LMCA reocel at	good	7
25	07-02-2013	0.00	32	0.2	1	1	2	2	ISR OF LCMA	3	15.0					
25	06-05-2013	0.00	32	0.6	0	0	1		not done	3	10.0					
26	14-02-2013	1.00	57	5.1	15	59			PTA with cover	3	45.0	2	1	new areas at 6 m	good	16
26	16-05-2013	0.00	29	1.7	3	3	4		not done , proba	3	37.5					
26	26-08-2013	1.00	32	12.7	1	3	2	2	new documenta	3	30.0					
26	03-06-2014	1.00	24	12.1	4	6	5	2	ULRa 60% ISR	3	27.5					
27	19-02-2013	1.00	15	14.7	20	22			nil	3	20.0	0	0			0
28	06-03-2013	0.00	5	0.15	3	3			PAG followed b	3	20.0	1	1	not done	good	14
28	06-06-2013	0.00	16	0.6	0	0	0		not done							
28	15-05-2014	0.00	10	0.1	3	3	0		not done	3	5.0					
29	07-03-2013	1.00	8	2.12	0	0			URRA,CA, LSC	3	25.0	1	2	nil	good	18
29	03-06-2013	0.00	2	1.4	0	0	0	2		5	15.0					
29	12-12-2013	0.00	3	0.2	0	0	0	2	LIMA 70% sten	3	10.0					
29	10-03-2014	0.00	5	0.2	0	0	0		not done	3	4.0					
29	04-09-2014	0.00	4	0.2	0	0	0		not done	3	4.0					
30	27-02-2013	0.00	14		0	0		2	PAST INTERVI	1	22.5	1	2	nd	good	13
30	15-07-2013	0.00	62	1	0	0	3		not done	1	17.5					
30	17-03-2014	0.00			0	0			not done	1	7.5					
31	07-03-2013	1.00	24	17.4	17	20			nil	3	35.0	0	0			0
32	11-03-2013	1.00	89	21	6	9			aCTIVE DS SO	3	20.0	3	1	repeted ISR	good	15
32	24-02-2014	1.00	73	45.5	5	8			NOT DONE DUE TO ACTIVITY, PET CT DONE							
33	14-03-2013	1.00	70	13.7	8	13			LSCA and DTA	3	35.0		0			0
34	08-04-2013	1.00	75	9.3	3	7			CAG + PAG + I	3	37.5	1	2	non progreesive	good	16
34	05-07-2013	1.00	36	8.9	0	0	1		not done	3	27.5					
34	23-12-2013	1.00	46	12.4	0	2	3		not done	3	15.0					
34	27-03-2014		74*	99*	0	4	3		notdone	3	5.0					
34	21-07-2014	1.00	51	7.3	0	1	2	2	all stents patent,	3	4.0					
35	08-04-2013	1.00	73	54.2	8				angio not done d	3	35.0	2	1	90% LSCA ISR	good	15
35	16-07-2013	1.00	33	21.9	0	3	1	1	angi odone ist tir	5	20.0					
35	12-03-2014	0.00	4	0.1	0	0	0		not done, likely	3	5.0					
35	16-07-2014	1.00	85	42.1	1	4	4	1	LSCA 90% ISR	3	35.0					
37	15-05-2013	1.00	30	8.1	3	5			PTA STENTIN	5	37.5	1	1	ND	good	17
37	13-06-2013	0.00	5	0.2	0	0	0		not done	5	20.0					
37	13-08-2013	0.00	2	0.1	3	3	3		not done	5	35.0					
37	31-10-2013	0.00	4	0.2	5	5	5	1	LSCa 50% reste	5	25.0					
37	30-01-2014	0.00	18	13.9	0	2	0		not done	3	12.5					
37	14-07-2014	1.00	32	9.4	0	1	1		not done	3	7.0					
37	09-10-2014	0.00	18	8	1	1	0		not done	3	10.0					
38	16-05-2013	1.00	33	6.29	14	15			recan LCCA exc	3	30.0		0			
39	09-04-2103	0.00	17	1.84	11	11			PTA with st to l	3	50.0	2	1	LSCA, LCCA 5	defaulted	19
39	27-05-2013	1.00	25	22.2	1	3	2		not done	3	47.5					
39	08-07-2013	1.00	35	33.3	1	3	2		NOT DONE	3	45.0					
39	12-11-2014	1.00	17	16.4	8	10	8	1	LSCA ISR, LCC	3	25.0					
40	12-06-2013	1.00	67	12.7	1	6			RRA ,SMA PTA	3	50.0	2	1	ND	good	17
40	29-08-2013	0.00	35		0				not done	3	45.0					
40	11-11-2013	0.00	22	3.2	0	0	1		not done	3	27.5					
40	13-02-2014	0.00	13	0.7	0	0	0	2	nil	3	17.5					
40	24-11-2014	1.00	66	12	4	6	7	2	angio diffuse ISI	3	5.0					
41	10-06-2013	1.00	32	17	0	2			PTA to DTA go	3	25.0	1	2	only doppler do	good	14
41	07-10-2013	1.00	23	10.1	3	4	3		not done	3	25.0					
41	28-12-2013	0.00	4	2.1	0	0	0		not done	3	17.5					
41	28-04-2014	0.00	9	8	0	1	0		not done	3	9.0					
41	02-08-2014	0.00	12	3.4	0	0	0		not done only d	3	7.5					
42	14-06-2013	1.00	47	17	25	29			PTA with stentir	3	25.0	2	1	both angio new lesions with LSC		16
42	10-02-2014	1.00	83	47.7	0	3	3	1	LCCA (new), LS	3	25.0					
42	16-10-2014	1.00	49	57.5	0	3	2	1	LVA 90% sten r	3	12.5					
44	12-03-2013	0.00	7	2.46	0	0			PTA stent to the	3	30.0	2	2	at 6 mo imld lsr	good	6
44	20-06-2013	0.00	15	17.3*	0	2	0		not done	3	17.5					
44	11-09-2013	1.00	14	27.5	7	10	7		not done	3	32.5					
45	19-06-2013	1.00	28	12.2	0	2			nil, now creat 0.	1	7.5	1	0	nd	good	15
45	23-09-2013	0.00	5	5.9	0	0			NOT DONE	1	8.5					
45	10-09-2014	0.00	6	0			3			7	5.0					
46	21-06-2013	0.00	26	1.03	0	0			may 2012 b/l CI	3	25.0	1	0			14
46	02-09-2013	2.00	32	0.8	1	1	2	1	IMA occl, PTA	3	7.5					
46	12-01-2015	0.00	27	1.17	0	0	0		ima stent patent	3	10.0					
47	27-06-2013	1.00	44	32.4						5		3	2	ND	GOOD	18
47	03-10-2013	0.00	1	0.2	0	0	0	2	RSCA, LCCA, I	3	10.0					
47	06-03-2014	1.00	45	13.7	1	3	3		not done	3	10.0					
47	04-04-2014	1.00	32	12	1	3	2		NOT DONE	3	10.0					
47	18-08-2014	1.00	42	14.3	0	2	2		not done	3	6.6					
47	15-12-2014	1.00	28	14.6	1	3	2		NOT DONE	3	7.5					
48	08-07-2013	1.00	50	11.1	14	16			NIL DUE TO A	3	40.0	3	2	ND	GOOD	9
48	23-09-2013	1.00	59*	10.3	0	1	2	2	same as beofre	3	35.0					
48	16-01-2014	1.00	68*	33.1	3	6	6		not done	3	32.5					
48	19-04-2014	1.00	57*	24.5	0	3	2		not done	3	22.5					
49	01-07-2013	0.00	1	0.407	7	7			nil	7	0.0	1	2	new LAD OCCI	GOOD	13
49	01-07-2013	0.00	3	0.4	0	0	0	2	progrsed diseas	6	20.0					
49	29-03-2014	0.00	16	0.4	0	0	0	2	ascaort, InA, LS	6	4.0					
50	25-06-2013	1.00	105	75.4	10	16			had undergone C	3	40.0	2	1			5
50	28-08-2013															
51	22-07-2013	0.00	15	1.43	12	12			Recan/st LSCA,	3	27.5	1	0	LSCA 50% ISR	GOOD	7
51	28-10-2013	0.00	5	11.6	0	1	0		not done	3	20.0					

51	06-02-2014	0.00	3	1.3	0	0	0		not done		3	10.0						
52	12-04-2013	1.00	44	4.43	14	15			not done due to		3	22.5	1	2	1ST FUP DTA S	GOOD		12
52	08-07-2013	1.00	33	19.1*	5	7	6	1	progression of IE		3	50.0						
52	24-04-2014	0.00	18	0.5	0	0	0	2	same as beofre,		3	17.5						
53	15-07-2013	1.00	76	25.7	8				not dne due to a		6	35.0	1	0	ND	DEFULTER		11
53	21-10-2013	1.00	59	45	2	5	5		not done		6	25.0						
53	20-06-2014	1.00	32	17*	1	3	2		not done		6	20.0						
54	08-07-2013	1.00	35	10.2	18				LA /acla neg		1	15.0		0	ND			3
54	03-10-2013	0.00		7.3	0	1	0		not done		1	17.5						
55	29-07-2013	1.00	65	15	24	28			DTA, IRAA WA		3	30.0	1	2	ND	GOOD		8
55	12-12-2013	1.00	74	12	0	2	3		not done		3	25.0						
55	20-03-2014	1.00	88	25	0	3	3				3	17.5						
56	30-07-2013	1.00	45	17.1	12	4			PTA with st to n		5	30.0	2	2	STABLE ,NO P	GOOD		13
56	29-03-2014	1.00	25	17.1	0	2	1		not completed d		3	5.0						
56	18-08-2014	1.00	57	13.7	0	2	2	2	all stent patent		3	5.0						
57	05-08-2013	1.00	6	0.15	11	11			not done		3	20.0	1	0	ND	GOOD		2
57	08-10-2013	0.00	8	0.2	0	0	0	2	1st time h/l RA		3	20.0						
58	20-06-2013	0.00	8	18.2	0	3			not imaged		3	35.0		0				0
59	04-09-2013	1.00	28	7.9	0	1					3	10.0		0				0
60	09-08-2013	1.00	48	28	17	20			due to financial		6	37.5	2	2	nd	GOOD		15
60	03-09-2013	1.00	16	17.9	0	2	0		slective angio fo		6	27.5						
60	31-10-2013	0.00			0				not done		6	32.5						
60	27-01-2014	1.00	40	46.3	0	3	1	2	patent LCCA-LI		1	15.0						
60	30-01-2014	1.00	49	20.9	0	2	1		not done		1	7.5						
60	28-04-2014	1.00	99	20		2	3		not done									
60	20-06-2014	1.00	58	11.7	0	2	2		not done		6	5.0						
60	20-11-2014	1.00	69	16.3	0	2	3		not done		6	2.5						
61	03-09-2013	1.00	55	7.9	8	9			nil		3	50.0		0				0
62	23-09-2013	1.00	38	1.5	11	11			cornary a, lsca,		3	25.0	1	2	stable non progr	GOOD		9
62	10-01-2014	0.00	16	1.4	0	0	0		not done		3	17.5						
62	07-07-2014	0.00	27	0.9	0	0	1	2	all stents patent		3	1.3						
63	04-10-2013	1.00	80	3.47	1				lra PTA with ste		3	22.5	1	1	PROGRESSED	GOOD		11
63	04-01-2014	1.00	9	0.2	12	12	12	1	narrowing of arc		3	45.0						
63	14-03-2014	0.00	5	0.2	0	0	0		not done		3	37.5						
63	09-06-2014	0.00	16	0.7	4	4	4	1	70% discrete ISI		3	25.0						
63	11-09-2014	0.00	9	0.2	0	0	0		not done		3	17.5						
64	10-10-2013	0.00	17	2	0	0			nil		6	30.0	1	0	ND	GOOD		10
64	06-02-2014	1.00	39	6.1	0	0	2		not done		6	12.5						
64	15-05-2014	1.00	30	9.5	0	1	2		not done		6	5.0						
64	18-08-2014	0.00	18	48*	0	2	0		not done		6	7.5						
65	11-09-2013	1.00	38	12.7	4	6			no as disease act		6	50.0		0				
65	11-09-2013	0.00	5	3	0	0		2	same as before		6	40.0						
66	15-10-2013	1.00	45	12.5	4				not done due to		3	40.0	1	0	not done	GOOD		9
66	09-04-2014	0.00	26	0.9	0	0	0		not done, celiac		3	30.0						
66	07-07-2014	0.00	26	2.8	0	0	0		not done		3	20.0						
67	10-10-2013	0.00	10	0.173	0	0			CIA PTA with		6	20.0	1	0	ND	RPTD DEFAUL		10
67	17-03-2014	0.00	32	1.8	0	0	1		not done		6	10.0						
67	17-03-2014	0.00	32	1.8	0	0	1		not done due to		6	10.0						
67	02-08-2014	0.00			2						7	50.0						
68	23-11-2013	1.00	18	12.8	6	8			nil due to financ		3	20.0	3	1	ISR RRA 60%	GOOD		12
68	04-04-2014	1.00	59	41.3	0	3	2		not done		3	20.0						
68	07-08-2014	1.00	44	26.2	0	3	2		not done		3	12.5						
68	24-11-2014	1.00	57	31.2	3	6	2	1	ISR LRA, rest R		3	22.5						
69	30-11-2013	1.00	25	3.4	7	7			PTA with stent t		3	20.0	2	0	LSCA diffuse IS	DEFULTED ON		9
69	21-08-2014	1.00	50	10.3	4	6	6		not done		3	10.0						
70	09-12-2013	1.00	60	70.3	2	5								0	STABLE AT LAST FUP			0
71	08-12-2013	1.00	92	15.5	26	28			angio not done d		3	35.0		0				0
72	10-01-2014	1.00	40	11.2	23	25			not done due to		6	50.0	2	0	ND	STEROID ERR		12
72	13-03-2014	0.00	6	5.4	0	0	0		not done		6	40.0						
72	05-06-2014	0.00	13	15.5	0	2	0		not done, financ		6	30.0						
72	31-07-2014	1.00		20	0	2			not done		6	27.5						
72	15-09-2014	1.00	33	11.2	0	2	1		not done		6	22.5						
72	08-12-2014	1.00		13.6	0	2			not done		6	10.0						
73	20-01-2014	1.00	26	13.9	11	3			PTA with covere		3	10.0		0				0
74	03-12-2013	1.00	24	50.3	5				RRA, abd thorac		3	35.0	1	2	all patent at 10 n	GOOD		10
74	20-01-2014	1.00	1	44	1	4	1		not done ,laparas		3	10.0						
74	01-05-2014	0.00	39	1.8	0	0	1		nil not done		3	22.5						
74	13-10-2014		47	20.6*	0	2	1	2	all vessel patent		3	7.5						
75	05-01-2014	1.00	9	3.4	4	4			dilat ans st of LS		6	25.0	1	2	ND	GOOD		6
75	24-04-2014	1.00	20	25.6	0	3	0		not done		6	5.0						
75	24-07-2014	1.00	42	25.3	0	3	1		not done		6	5.0						
75	24-07-2014	1.00	42	25.3	0	3	1		not done		6	5.0						
76	07-01-2014	1.00	12	7.87	8	9			angiop not done		3	60.0	2	0		GOOD		10
76	31-03-2014	1.00	45	35	0	3	2		not done		3	45.0						
76	09-06-2014	1.00	20	6.4	0	0	0				3	40.0						
76	21-07-2014	1.00		10.9	0	1			not done, financ		3	35.0						
76	20-11-2014	1.00	28	16.3	0	2	1		not done		3	25.0						
77	06-02-2014	1.00	5	6.2	19	19			nil		3	30.0	1	2	nd	good		7
77	22-07-2014	0.00	5	2.2	2			2	same as before,		3	22.5						
78	04-02-2014	1.00	33	35.8	3	6			RCCA--> RICA		3	45.0	2	1	ISR RSCA 80%			7
78	06-09-2014	1.00	13	37.2	6	9	6	1	ISR of 80% of R		3	20.0						
79	06-02-2014	1.00	16	2.19	6	6			nil		3	20.0	2	0	ND	GOOD		8
79	10-04-2014	1.00	61	13.8	0	2	0		NOT DONE		3	17.5						
79	14-07-2014	0.00	34	1.7	0	0	1		not done		3	12.5						
79	09-10-2014	1.00	60	32.5	0	3	3		not done		3	10.0						
80	11-01-2014	1.00	42	17.9	12	15			recan + life st LS		3	50.0	1	2	stent minor diffi	GOOD		10
80	08-05-2014	1.00	34	23.5	0	3	1		notdone		3	37.5						
80	20-11-2014	0.00	7	6.4	0	0	0	2	abd wall stent, C		6	22.5						
81	12-02-2014	1.00	86	14.8	0	2			RRA covered st		3	30.0	1	0	nd	good		10
81	07-07-2014		32		0		1		not done		3	22.5						
81	08-12-2014	1.00	32	19.6	0	2*	1		not done		3	15.0						
82	06-02-2014	1.00	50	3.1	3	3			recan with stent		3	30.0		0				0
83	18-02-2014	1.00	79	38.4	11	14			recan of RVA, R		3	50.0		0				0
84	19-02-2014	1.00	34	23	1	4			PTA WITH STE		3	27.5	3	0	ND	GOOD		8
84	01-10-2014	1.00	32	28.2	1	4	2				3	10.0						
84	16-04-2104	1.00	49	48	0	3	2		not done		3	40.0						
85	02-10-2013	1.00	29	15	7	9			planned no finar		3	30.0	1	0	ND	GOOD		12
85	24-02-2014	1.00	57	1.3	0	0	2		not done		3	27.5						
86	05-03-2014	0.00	1	0.173	0	0			nil requd		3	75.0		0				
87	25-11-2013	1.00	17	5.9	4	4			LSCA recan+st,		3	25.0	1	2	ALL PATENT ,I	GOOD		9
87	04-03-2014	0.00	12	5	0	0	0		not done		3	17.5						
87	31-08-2014	0.00	11	4.1	0	0	0	2	all stents patent		3	17.5						
88	05-03-2014	1.00	33	8.38	17	18			PTA WITH POI		3	30.0		0				0
89	01-02-2012	0.00	5	9.58	4*	5	4	1	lsca stnt occ , re		1	20.0	1	1	ISR at 3 months LSCa			168
89	01-08-2013	0.00	19	13.8	3	4	3	1	rsca stent occlus		1	20.0						
89	06-03-2014		25	17.9	0	0			nil now		1	5.0	1		ISR at 3 months LSCa			
90	16-08-2011	1.00	85	19					PTA with stentii		3	30.0	1	1	isr in coronary at 23 mo, rtsca dil			27
90	09-11-2013	1.00	18	9.7	1	2	1	1	cornoray, rsca st		1	50.0						
91	16-07-2012	1.00	35		8	8			rsca pta with ste		3	60.0	1	2	stent patent rsca	good		23
91	19-06-2014	1.00	31	8.5	0	1	1		not done		3	9.0						
91	04-12-2014	1.00	21	9	0	1			not done		3	15.0						
92	27-10-2009	0.00	5	1.6	0	0	0		rra stenosis stent		7	0.0	1	2	nil	good		47
92	27-11-2011	0.00	3	1.13	0	0	0	1	isr rra stenosis		3	50.0		1				
92	22-07-2013	0.00	14	6	0	0			eariler RRA sten		3	1.0	1		nil			
93	01-08-2013	1.00	51	31.1	0	3			RCA recan cove		3	50.0	1	2	cant say			108
94	29-03-2014	1.00	50	27.4	12	15			PTA STENT RS		3	30.0		0	patent stents	good		0
95	29-03-2014	1.00	37	14	2	4					7	0.0		0				0
96	29-03-2014	1.00	38	18.6	3	6			PTA st of RCCA		3	15.0	1	1	only rptd ISR of LSCA stent, RC			48
96	17-04-2014	1.00	32	17.2	3			2	only diffuse ISR		3	15.0						
97	04-04-2014	0.00	10	0.2	0	0			PTA WITH ELI		3	25.0	1	2	patent LSCA	good		6
97	24-09-2014	0.00	11	1.2	0	0	0	2	patent LSCA sta		3	10.0						
98	05-04-2014	1.00	53	5.8	0	0			PTA st to RCIA		5	15.0	2	1	not done	good		8
98	04-09-2014	0.00	6	0.2	1	1	1		not done - outsid		5	5.0						
98	08-12-2014	0.00	5	0.2	1	1	1				3	5.0						
98	24-12-2014	1.00	60	35	3	5			outside esr ep raised									
99	09-04-2013	1.00	70	18.2	11	14			NI		6	20.0	2	2	NIL	good		18
99	05-06-2014	0.00	18	3.4	0	0	0		not done		7	20.0						
99	14-08-2014	1.00	38	21	3	6	4		not done		7	15.0						
99	15-09-2014	1.00	25	6.7	1	2	2		not done		7	20.0						
99	16-10-2014	0.00	11	5.2	3	4	4	2	only PAG done		7	22.5						
100	12-04-2014	1.00	25	34.5	0	3			DTA wall stent		5	7.5	2	1	angio progressa	good		4
100	12-08-2014	0.00	4	0.2	3	3	3	1	diffuse isr overla		7	7.5						
101	12-04-2014	1.00	44	49.1	18	21			not done- active		3	22.5		0				0
102	23-04-2008	1.00	30	17				1	lmca isr outside		1	17.5	2	1	RRA denovo at	good		84
102	01-01-2010	1.00	37	12.1	0	2	1	1	LMCA 90%ISR		3	25.0	2	1	RRA denovo at 52 mo, 5 times IS			0
	12-12-2012	0.00		1.91	0	0	0	1	LMACa total oc		5	5.0		1				
102	31-03-2014	1.00	34	4.61	0	0		1	POBA LMCA (I		3	25.0	2	1	RRA denovo at 52 mo, 5 times IS			0
103	15-04-2014	1.00	37	11.1	23	25			nil		3	35.0	1	0	nd	good		3
103	07-07-2014	0.00	22	5.2	0	0	0		not done		3	17.5						
105	09-02-2014	0.00	3	3.25	4	4			patent RRA but		3	10.0	2	2	RRA stent ist dto technical reason			144
105	19-05-2014	0.00	4	0.9	0	0			not done		3	17.5						
105	04-09-2014	0.00	8	0.9	1	2	0	2	CA minor narro		3	9.0						
106	01-05-2014	1.00	59	7.26	5	6			nil		3	25.0		0		good		4
106	08-09-2014	1.00	85	99	0	3	3		not done									
107	10-02-2014	1.00	79	11.6	8	10			not done		7	12.5		0				
108	15-05-2014	1.00	39	67.8	1	4			fiancial constrai		6	30.0		0				0
109	06-05-2014	1.00	42	4.45	0	0			nil		3	10.0	1	2	stable disease			6
109	15-11-2014	0.00	10	4.7	0	0	0	2	B?I RA minor IS		3	7.5						
110	08-05-2014	1.00	68	85.1	21	24			ds active, financ		3	60.0	2	2	awaited	good		7
110	14-07-2014	0.00	4	4.3	0	0	0	2	done last month		3	52.5						
110	16-10-2014	0.00	19	13.5	0	2	0		not done		3	40.0						
110	17-12-2014	1.00	27	8.2	3	4	4		pending									
111	16-05-2014	1.00	20	11.4	5				RRA recan, mild		3	30.0	1	0	nd	good		3
111	14-08-2018	0.00	4	0.6	0	0	0		not done		3	22.5						
112	26-05-2014	1.00	84	55.1	26								1	2	stable all patent	good		3
112	30-08-2014	0.00	17	2.7	0	0	0	2	no proegrassion		3	27.5						
113	05-06-2014	1.00	47	64.7	11				LSCA PTA with		3	45.0	1	1	acitve	good		4
113	06-10-2014	1.00	10	8.1	4	5	4	1	left LSCA stent		3	27.5						
114	09-06-2014	1.00	15	1.05	3				nil		3	20.0		0	no progression			

115	16-06-2014	0.00	10	2	0	0			PTCA with kissa		3	50.0		0				
115	16-10-2014	0.00	25	3.6	0	0	0	2	LMCA 80 befor		3	37.5						
117	23-06-2014	1.00	41	3	13				PTA /stent LSC		5	15.0	1	1	active LAD, LM	good		6
117	26-07-2014	0.00	4	0.1	0	0	0		nil		5	12.5						
117	26-08-2014	0.00	12	0.7	0	0	0		not done		5	10.0						
117	12-10-2014	0.00	5	0.1	1	1	0	1	tight ISR LM, os		5	10.0						
117	12-10-2014	0.00	1	0.17	1	1	0	1	LMCA tight ISR		5	10.0						
118	19-05-2014	1.00	6	16.7	1				PTA with spic st		3	25.0	1	0		good		4
118	15-09-2014	0.00	7	8.8	0	1	2		not done		3	22.5						
120	17-07-2014	1.00	81	21.4	20				nil as active ds		6	40.0		0				
121	10-07-2014	1.00	44	87.5	4				axillobrachail sta		5	25.0	2	1				48
122	19-07-2014	1.00	59	8.57	3				not done		3	25.0		0				
124	04-09-2014	1.00	40	2.5	5				nil		6	50.0		0				
128	10-11-2014	0.00	20	5.7	0	0	0	2	no progression o		3	22.5						
128	21-08-2104	1.00	42	13.6	7				no planned next		3	30.0		0	angio stable	good		3
129	25-05-2011	1.00		20.1	2	4			in march 2010 st		3	20.0	2	1	1a mid lsca, pate	good		54
129	17-01-2012	1.00	88	51	3	5	5	nil	nil		3	10.0						
129	10-03-2013	1.00	36	12.4	5	7	6	denovo mid lsca	poba stent to mi		3	20.0						
129	02-06-2014	1.00	21.8	42	0	3	1	3	nil		3	12.5						
130	01-02-2012	1.00	9	31.8	1	4	1	1	lcca, lra, ca poba		3	40.0	2	1	1	good		35
130	01-08-2012	0.00	3	0.1	3*	0	0	2	nil		5	5.0						
130	18-12-2013	1.00	25	13.9	5*	2	1	1	lcca poba,	3.5,3 1gm		12.5						
131	01-07-2009	1.00	125	35.9					nil, ectasia, stend		1	30.0	2	1	inc in ectasia, A	non compliant		62
131	25-02-2010	1.00			4			0	nil		1	30.0						
131	16-09-2013	1.00	102	96	0	3	3	0	nil	1--> 3		22.5						
131	13-03-2014	1.00	66	46.6	0	3	2	exclusion stent	nil		3	20.0						
131	12-05-2014	0.00		0	infection				nil									
131	11-09-2014	0.00	60	40	0	3	2	0	nil		3	7.5						
132	19-06-2012	1.00	12	2.2					yes		3	35.0	2	2	1	good		17
132	05-09-2013	0.00	22	11.7	0	2	1	1	CA 30 to 90% p		3	45.0						
132	22-05-2014	1.00	19	2.6	4	4	4	2	renal patent at 8		3	10.0						
132	03-09-2014	1.00	9	0.78	4	4	4	1	denovo RSCA, d		3	10.0						
132	21-11-2014	0.00		2.9	4*		4	0	most likely isr		3	10.0						
133	27-07-2010	1.00	32	4.43					LSCA, DTA, LC		3	35.0	2	1	diffuse ISR of L	good		46
133	15-10-2012	1.00	57	6.03	4*	5	5	1	minor isr lcca, d	3-->5		15.0						
133	24-01-2013	0.00	5	0.1	0	0	0	0	nil		5	12.5						
133	21-10-2013	0.00	29	5.46	0	0	0	0	nil		3	5.0						
134	24-11-2008	1.00	15	51					nil		3	50.0	2	2	minor lesion dis	good mmf levels		72
134	01-03-2009	1.00	30	33.3	0	3	1	1	PTCA RCA, Re		3	40.0						
134	18-08-2010	1.00	30	53.1	0	3	1		nil		3	27.5						
134	28-12-2011	1.00	35	41	0	3	1	1	lca, rsca patent,		3	9.0						
134	15-10-2012	1.00	40	26.7	0	3	2	0			3	7.5						
134	19-12-2013	1.00	32	17.7	0	2	1	0	nil		3	7.5						
134	19-06-2014	1.00	34	18	0	2	1	0	nl		3	5.0						
134	11-12-2014	1.00	34	17.3	0	2	1	0	nl		3	5.0						
135	10-05-2006		23	36.4				0	nephrectomy		1	25.0	2	2	RSCa new inv in	GOOD		108
135	16-04-2012	1.00		14.5	0	2	0	1	nil , lter lsca sten		3	7.5						
135	08-11-2013	1.00	15	36	0	3	0	0	ni		3	5.0						
135	16-06-2014	1.00	13	37.2	0	3	0	0	nil		3	15.0						
136	07-06-2008	1.00	63	3.54					lsca stent, lcca p		1	40.0	2	1	LSCA rptd ISR,	good		108
136	27-01-2010				0	3					3	20.0						
136	21-11-2011	1.00						1	poba to lsca isr at 30 mo, 36 mo, denovo CA									
136	21-11-2012	0.00	20	4.49	0	0	0	3	nil, poba to ISR		3	20.0						
136	22-08-2013	0.00	16	4.39	0	0	0	3	poba was done o		3	10.0						
136	18-12-2013	1.00	39	13.7	4*	6	5				3	20.0						
136	10-05-2014	0.00	16	4.3	0	0	0	1	edge isr of lsca,	covered stent								
137	29-07-2008	1.00	65	24.9					lscaisr		3	30.0	2	2	yes	good		60
137	01-08-2011	1.00	114	22.1	3	6	6		pd		3	12.5						
137	01-02-2012	1.00	53	9.51	1	4	4	1	patent LSCa at 4		3	9.0						
137	01-08-2013	1.00	41	13.6	0	2	2	0	nd		3	5.0						
138	12-01-2009	1.00	15	5.82					pta stent lsca		3	30.0	2	1	rptd difuse isr di	defualted once a		72
138	17-02-2010	0.00	20	7.5	0	0	0	0	nd		3	7.5						
138	12-01-2011	0.00			0	0	0	2	patent lsca at 24		3	10.0						
138	17-11-2012	1.00	33	17.5	4*	6	5	1	90% isr extendir		3	50.0						
138	07-05-2013	0.00	20	5.55	4*	4	4	1	100% isr lsca	3--> 5		10.0						
138	15-10-2013	0.00	5	0.13	0	0	0	0	0	0	5	5.0						
138	18-12-2013	0.00	23	4.01	0	0	0	1	sr 75% but frree		3	4.0						
139	21-05-2011	1.00	40	8.65	0	1	0		pta st of rra, lra		3	5.0	1	2	new Cad ,subseq	good		35
139	01-11-2012	0.00	20	0.5	0	0	0	0	0	0	3	5.0						
139	25-06-2013	0.00		9.96	0	1	0	0	nil		3	5.0						
139	29-06-2014	0.00	4	1.4	0	0	0	2	patent renal sten		3	4.0						
140	01-01-2010			0.599					dta, lcca rcca pta		3	2.5	2	2	RCA, b/l RA ne	good		50
140	01-03-2011	0.00	5	1.43	0	0	0	0	b/l rra stent with		3	10.0						
140	01-09-2011	0.00		0.539	0	0	0	2	stents patent		3	7.5						
140	12-09-2013	0.00	1	1.96	0	0	0	0	stent patent eag		3	5.0						
140	09-12-2013	0.00	7	1.23	0	0	0	0	0	0	3	2.5						
140	12-02-2014	0.00	7	2.36	0	0	0	0	nil		3	2.5						
140	16-10-2014	1.00	9	1.82	0	0	0	1	fad isr 80%, 50%		3	30.0						
141	03-01-2013										3	20.0	1	0				
142	15-09-2009		30	0.168					recan LICA, sten		1	35.0	1	2	2	defaulted once		36
142	29-10-2012	0.00							actiity not asessed due to urospesis									
142	31-05-2012*	1.00	61	30	2	3	4	2	stent patent no n		6	25.0						
143	09-04-2009	1.00	125	65	12	15	15		nil		3	45.0	1	1	1	good		48
143	08-11-2009	1.00	40	12.7	0	2	1		rsca recan		3	35.0						
143	04-07-2013	0.00		4	0	0	0	1	nil 2010 occlude		3	40.0						
143	18-11-2013	0.00		13.9	1	2	0	0	nil		3	15.0						
143	02-06-2014	0.00		13.8	0	2		1	occlusion of rsca		3	15.0						
143	02-10-2014	0.00						0	nil		3	10.0						
144	16-09-2012		1	1.14					lsca, lcca stent,		3	30.0	1	2				15
144	19-03-2013	0.00	16	8.4	0	1	0	1	ULRA 70% ostia		3	20.0						
144	19-03-2014	0.00	1	1.04	0	0	0	2	patent stents		3	7.5						
145	27-07-2012	1.00	6	0.26	12	12	12		rt cca		4	12.0	1	1				24
145	20-11-2012	0.00	5	0.67	0	0	0	2	bl cca patent		4	5.0						
145	17-04-2013	1.00	65	3.55	4	7	7	0	nil		3	40.0						
145	08-11-2013	1.00	5	0.67	1	1	1	1	rcca patent lcca		3	20.0						
145	11-08-2014	0.00	62	10.8	1	1	3	0			1							
146	19-03-2012	1.00	5.73						poba rva, LCCA		3	55.0	1	0	pending	good		26
146	21-09-2012	0.00	2	0.19	0	0	0	al stents patent	nd all stent patei		3	25.0						
146	17-09-2013	0.00	18	11.3	0	2	0	0	all lcca, rsca,inc		3	5.0						
147	05-03-2012		6	2.8					ca, lrra stented		6	30.0	1	2				14
147	03-09-2012	1.00	74	37.1	3	6	6				3	30.0						
147	31-01-2013	0.00	19	7.6	0	0	0				3	25.0						
147	07-10-2013	0.00	59	47.4	3	2		1	lrra diff isr, ca		3	20.0						
148	09-09-2009	1.00	30	7.76					sma, ca, rra sten		3	30.0	1	1	minor ISR	good		63
148	04-08-2010	1.00		11.8	1	2		1	CA, URRA, LR		3	10.0						
148	23-02-2011	0.00	48	3.79	1	1	3	0	nil		3	10.0						
148	09-04-2013	0.00	30	1.68	0	0	1	0	focl ca, sma isr,		3	5.0						
148	08-11-2013	0.00	21	4.64	0	0	0	0	0		3	2.5						
148	13-08-2014	0.00	7	3.4	0	0	0	0	nil		3	2.5						
149	12-01-2010	0.00	20	3.09	3	3	3		lura, llra, rsca pa		1	30.0	1	1	isr	defaulted in bets		56
149	08-08-2010	0.00	31	0.28	4*	4	5	1	rsca isr, lra isr	1-->3		40.0						
149	12-03-2012	1.00	35	8.7	4	5	5				3	35.0						
149	01-09-2012	0.00	16	1.8	2	2	2	1	isr rsca, ulra, llra		3	35.0						
149	21-03-2013	1.00		17	0	2					3	20.0						
149	08-08-2013	0.00	16	9.44	0	1	0	0			3	20.0						
149	06-10-2014	0.00	16	9.36	5*	6	5				3	15.0						
150	01-06-2011	1.00	80	31.8					rcca, lcca stent		3	35.0	3	1	rptd isr, stenoss	good		38
150	09-09-2012	1.00	30	17.3	3*	9	8	1	POBA LCCA is		3	30.0						
150	30-05-2014	1.00	42	21.5	3	6	5	1	ISR LCCA	3--> 5		5.0						
151	12-04-2010	0.00	42	2.97	0	0	0		recan stnet of rra		3	5.0	1	2	nil	good		57
151	01-11-2011	0.00	42	2.8	0	0	0	2	patnt rra		3	5.0						
151	10-10-2013	0.00	34	0.9	0	0	0	2	nil		3	0.0						
151	22-12-2014	0.00	34	0.7	0	0	0	0	nil		3	0.0						
152	15-09-2010							1	rra rean abd aort		3	5.0	1	2	minor focal ISR	good		11
152	27-04-2011	0.00	34	12.4	0	0		2	minor isrs		3	25.0						
152	15-08-2012	1.00	56	9.14	0	1	1	2	rra only foal isr		3	25.0						
153	01-05-2006	1.00	45	12					b/l cca , rsca sten		3	37.5	1	2	stable at 66 mo	good		96
153	29-05-2012	0.00	20	2.1	0	0	0	0	nil		3	0.0						
153	24-05-2013	0.00	17	0.25	0	0	0	2	stent patent dop		3	0.0						
153	25-08-2014	0.00	18	1.99	0	0	0	0	nil		3	0.0						
154	02-01-2010								no trt given		3	10.0	1	2	stable at 66 mo	good		44
154	03-03-2011	0.00	5	1.43	0	0	0		b/l renal pta		3	10.0						
154	09-09-2011	0.00	2	0.54	0	0	0	2	b/l renal patent a		3	10.0						
154	20-08-2012	0.00			0	0	0	0	nil		3	2.5						
154	12-09-2013	0.00	1	1.9	0	0	0	0	nil		3	5.0						
155	04-09-2007		20	0.22					angio no pta		1	40.0	1	2	nd	good		84
155	25-06-2013	0.00	9	0.244	0	0	0	0	nil		1	2.5						
155	03-07-2014	0.00	13	0.17	0	0	0	0	nil		2	2.5						
152	13-10-2014	0.00	13	1.25	0	0	0	0	nil		2	2.5						
156	18-11-2005		45	6.05					rra stent		1	40.0	1	2	nd	good		108
156	14-11-2013	0.00	5	2.6	0	0	0	0	nil		3	2.5						
156	01-05-2014	0.00	16	3.56	0	0	0	0	nil		3	2.5						
156	20-10-2014	0.00		4.6	0	0	0	0	nl		3	2.5						
157	22-09-2014											0.0		0				0
158											3	50.0		0				
159	27-06-2011										3	50.0		0				
159																		
159																		
160	01-01-2012	1.00	47	6.53					lsca, ca		6	30.0		0	nd	defaulted		5
160	23-08-2012	0.00	30		0		0		nil		6	17.5						
160	03-10-2013	0.00	20	4	0	0	0		nil		6	12.5						
160	22-05-2014	0.00	35	15.8	0	1	1		nil		6	12.5						
161														0				
	date of commen	0 stable						0 not done		1, 3 to be analysed together as one		0 no flup	0 na			good means com		0
		1 active						1 active		6 as separate		1 responding dis	1 angio progressed disease			rest non compli		0
								2 stable				2 refractory dise	2 angio non progressed disease					0

Annexure 4: Correlation data for cluster analysis of arteries in TA

	Pulmonary	Coronar	Rticar	Iticar	Rtccar	Itccar	Rtscla	Itscla	Rtverart	Itverart	Rtbrachi	Ascaorta	Arch	Desthora	Abdaorta	Coeart	Sma	Ima	Rtrenal	Itrenal	Rtcia	Itcia
Pulmonary	1																					
Coronar	-0.0057831	1																				
Rticar	0.109718	-0.0742383	1																			
Iticar	0.0431283	-0.1061158	0.35527986	1																		
Rtccar	-0.022226	0.04113165	0.0703559	0.05940885	1																	
Itccar	0.09752226	0.04206779	0.11895659	-0.0527554	0.54017744	1																
Rtscla	0.04855452	0.10715616	0.0583381	0.01421281	0.25456191	0.33634189	1															
Itscla	0.17220029	0.01054292	0.11260386	0.08973795	0.23336013	0.25562607	0.27651534	1														
Rtverart	0.09719915	-0.0712015	-0.0511896	0.03734721	0.30145197	0.25733374	0.33584274	0.18458422	1													
Itverart	0.07814992	-0.089021	0.09221434	0.13181057	0.16769577	0.21085375	0.23839898	0.20809293	0.26793536	1												
Rtbrachi	0.12681503	0.09193571	0.08236527	0.11773237	0.26575311	0.25132821	0.15077933	0.10660036	0.17829131	0.27398904	1											
Ascaorta	-0.0702012	-0.0068101	0.22287073	0.01731358	0.09059765	0.21038148	0.04770387	0.07697284	0.11445862	0.03137279	0.246	1										
Arch	-0.0705736	-0.0206336	0.21306686	-0.0431655	0.16835985	0.11636307	-0.0536476	0.01968677	-0.0731701	0.02679666	0.21815116	0.31856995	1									
Desthora	0.03673147	-0.1720894	-0.0920289	-0.0545475	0.06912133	0.19114837	0.05934532	-0.0107773	-0.076168	-0.0058162	-0.0640994	0.28057532	0.25348522	1								
Abdaorta	-0.0399219	-0.0600576	0.15857196	-0.0523106	-0.0689924	-0.1334181	-0.2992143	-0.1661386	-0.1478281	-0.0948209	-0.0703532	0.03358429	0.08718426	0.09908597	1							
Coeart	-0.0900672	-0.0305957	0.08078275	-0.026649	0.0117158	0.11166233	0.01364172	0.0225294	-0.1054332	-0.0053673	-0.0218541	0.00342183	-0.0977131	-0.0386781	0.08193775	1						
Sma	-0.0576979	0.05686864	0.2	-0.006083	-0.0829028	0.01662286	-0.0662043	-0.0871467	-0.1186134	-0.0110264	-0.068841	-0.0398349	-0.0790789	0.02469069	0.11953887	0.4536262	1					
Ima	-0.0404689	-0.0608806	-0.017311	-0.0247461	-0.0761545	-0.0946724	-0.1107039	-0.1509679	-0.0419591	-0.0448561	-0.0462693	-0.0476623	-0.0247461	-0.0748763	0.12901677	0.0252793	0.1627233	1				
Rtrenal	-0.1454194	0.16371225	0.07621094	-0.0323887	-0.2239428	-0.2590867	-0.0127789	-0.2460322	-0.1597605	-0.1441051	-0.1161922	-0.2120998	-0.0323887	-0.0875707	0.31056482	0.1341509	0.25252598	0.02178606	1			
Itrenal	-0.1265792	0.11883546	-0.0346043	-0.0494669	-0.2136352	-0.1510804	-0.1187103	-0.1198748	-0.1430813	-0.1318623	-0.106236	-0.2028815	-0.0494669	-0.0156762	0.28590901	0.12187309	0.15917967	0.01159308	0.52121869	1		
Rtcia	-0.082704	-0.0497673	0.17688728	-0.0505722	-0.0889328	-0.0069099	-0.1046778	-0.0589316	0.01071866	0.09166985	-0.0945578	0.07792372	-0.0505722	-0.018661	0.14197294	0.05166183	0.14150983	0.23026947	0.0445229	0.0846146	1	
Itcia	-0.0880451	-0.0618115	0.16320278	-0.0538382	-0.1025659	-0.0294245	-0.1833335	-0.210355	-0.0912871	-0.09759	-0.1006645	-0.020739	-0.0538382	-0.0357591	0.16553618	0.02566583	0.05272705	0.214498	0.07656639	0.05404748	0.56360186	1

Annexure 5

Turnitin Originality Report

Human Leucocyte Antigen-E (HLA-E) in Takayasu Arteritis by 161219021. Dm-rheumatology Dr Ruchika

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Introduction

7**Takayasu arteritis (TA) is a large vessel vasculitis** characterised **by inflammation** in arterial walls **of**

large arteries ultimately leading to stenosis and/or aneurysms in aorta and its main branches. There is an unmet need of studies addressing the genetic and immune mechanisms involved in pathogenesis of TA. Recent genetic studies including genome wide association studies have suggested a role of genetic polymorphisms in TA. Human leucocyte antigen class Ia has emerged as one of the most important candidate gene in TA. HLA-E, a class Ib acts as ligand for cells of both innate and adaptive immune system. It has a dual role in regulation of cytolytic activity of NK cell and cytotoxic T cells, the cells shown to be present in infilterate in arterial biopsy specimens of TA patients. With this justification, we decided to study HLA-E polymorphisms in our cohort of TA patients. Aim and objectives Aim: To study clinical associations of

6**HLA-E** variants **(HLA-E*01:01** i.e. ER **and HLA- E*01:03**

i.e. EG) in Asian Indian patients with Takayasu arteritis Objective 1: Primary objective was to study the clinical associations of

6**HLA-E** variants **(HLA-E*01:01** i.e. ER **and HLA-E*01:03**

i.e. EG) including disease susceptibility in Asian Indian patients with Takayasu arteritis. Objective 2: To study genotype- phenotype associations. Objective 3: To study association of HLA-E variants with disease free survival and its predictors in our cohort of patients with TA. Review of literature

7**Takayasu arteritis (TA) is** prototype **large vessel vasculitis** characterised **by granulomatous inflammation**