Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 2012

AL amyloidosis

Study of epidemiology, diagnosis and treatment with emphasis on heart involvement

SARA ROSENGREN

ACTA UNIVERSITATIS
UPSALIENSIS
2024

ISSN 1651-6206
ISBN 978-91-513-2023-6
urn:nbn:se:uu:diva-521524

UPPSALA
UNIVERSITET

Dissertation presented at Uppsala University to be publicly examined in H:son Holmdahlsalen, entrance 100/101, Akademiska sjukhuset, Uppsala, Friday, 15 March 2024 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Stefan Schönland (Heidelberg University, Germany).

Abstract

Rosengren, S. 2024. AL amyloidosis. Study of epidemiology, diagnosis and treatment with emphasis on heart involvement. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2012. 70 pp. Uppsala: Acta Universitatis Upsaliensis.
ISBN 978-91-513-2023-6.

AL (immunoglobulin light chain) amyloidosis is often associated with delayed diagnosis and thereby high early mortality that is not overcome by contemporary treatment. There is a need for diagnostic methods promoting earlier diagnosis, especially in patients with cardiac involvement. Progress has been made in the treatment of AL amyloidosis and prolonged survival has been reported from specialized referral centers. However, population-based reports are scarce regarding epidemiology as well as treatment outcomes. Aims of this thesis were to increase the knowledge of the epidemiology of AL amyloidosis, investigate new imaging methods for early diagnosis and prognostication in cardiac amyloidosis (CA), and evaluate treatment options with focus on patients with cardiac involvement.

In paper I we presented real-world long-term results of treatment with high dose chemotherapy for AL amyloidosis in Sweden. We could conclude that long overall survival (median 8.2 years, 95% CI 5.1-11.2) was reached with high dose chemotherapy, but with inferior outcomes in patients with cardiac involvement. Treatment related mortality was comparable to that reported from larger centers during this period and was decreasing from 23.8% to 7.8% during the studied time period.

In paper II we studied the accuracy of PET with the amyloid binding tracer ^{11}C-PIB for the diagnosis of CA. ^{11}C-PIB PET showed high accuracy in detecting CA, and affinity was higher for AL compared to transthyretin amyloidosis. We concluded that ^{11}C-PIB PET can be a useful method to rule in or out amyloidosis in patients with unexplained diastolic heart failure. Our results also indicated that ^{11}C-PIB PET can detect CA at an earlier stage than echocardiography and might be a useful tool for early diagnosis.

In paper III we studied the prognostic value of cardiac function parameters from ^{11}C-acetate PET in CA. We found that reduced myocardial external efficiency was associated with inferior survival in CA patients. However, the strongest prognostic parameter was lowered ratio of forward stroke volume and left ventricular mass, which was the only independently prognostic parameter in multivariable analysis.

Paper IV was a population-based epidemiological study in which we could determine the standardized incidence of systemic AL amyloidosis to 12.0 (95% CI 9.3-14.7) per million person-years for Uppsala County, without significant change during the period 2000-2020. The 5-year limited duration prevalence increased numerically, but without statistical significance. Prolonged overall survival was observed over time, and there was also a decrease in early mortality, indicating earlier diagnosis of especially patients with cardiac involvement.

Keywords: immunoglobulin light chain (AL) amyloidosis, high-dose melphalan, cardiac amyloidosis, positron emission tomography (PET), incidence, population-based

Sara Rosengren, Department of Medical Sciences, Haematology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-513-2023-6
URN urn:nbn:se:uu:diva-521524 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-521524)

The only true wisdom is in
knowing you know nothing.
Socrates

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Rosengren, S**., Mellqvist, U-H., Nahi, H., Forsberg, K., Lenhoff, S., Strömberg, O., Ahlberg, L., Linder, O., Carlson, K. (2016) Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation in Sweden, long-term results from all patients treated in 1994-2009. *Bone Marrow Transplantation,* 51(12):1569-1572.

II. **Rosengren, S**.*, Skibsted Clemmensen, T.*, Tolbod, L., Granstam, S-O., Eiskjaer, H., Wikström, G., Vedin, O., Kero, T., Lubberink, M., Harms, H. J., Flachskampf, F. A., Baron, T., Carlson, K., Mikkelsen, F., Antoni, G., Frost Andersen, N., Hvitfeldt Poulsen, S., Sörensen, J. (2020) Diagnostic accuracy of ^{11}C-PIB positron emission tomography for detection of cardiac amyloidosis. *JACC Cardiovascular Imaging,* 13(6): 1337-1347. * Equal first authors.

III. **Rosengren, S**.*, Skibsted Clemmensen, T.*, Hvitfeldt Poulsen, S., Tolbod, L., Harms, H. J., Wikström, G., Kero, T., Thyrsted Ladefoged, B., Sörensen, J. (2023) Outcome prediction by myocardial external efficiency from ^{11}C-acetate positron emission tomography in cardiac amyloidosis. *ESC Heart Failure,* 11(1): 44-53. * Equal first authors.

IV. **Rosengren, S**., Thelander, U., Mattsson, M., Carlson K. Population-based incidence, prevalence and survival of systemic AL amyloidosis in Sweden. *Manuscript.*

Contents

Abbreviations

AL	amyloid light chain
ATTR	amyloid transthyretin
ATP	adenosine triphosphate
AA	amyloid serum A
ASCT	autologous stem cell transplantation
AUC	area under the curve
BCL2	B-cell lymphoma 2
BMPC	bone marrow plasma cells
CA	cardiac amyloidosis
CI	confidence interval
CMR	cardiac magnetic resonance imaging
CO	cardiac output
CR	complete response
CRAB	hypercalcemia, renal dysfunction, anaemia, bone disease
CT	computer tomography
dFLC	difference between involved and uninvolved free light chain
iFLC	involved free light chain
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
ECV	extra cellular volume
EW	external work
FISH	fluorescence in situ hybridization
FLC	free light chain
FSV	forward stroke volume
FSVI	forward stroke volume index
HDM	high dose melphalan
ICD	international classification of diseases
IGVL	immunoglobulin light chain variable region
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range
IVS	interventricular septum
LGE	late gadolinium enhancement
LS	longitudinal strain
LV	left ventricle

LVM	left ventricular mass
EF	ejection fraction
MAPK	mitogen-activated protein kinase
MBF	myocardial blood flow
MCF	myocardial contraction fraction
MEE	myocardial external efficiency
MGUS	monoclonal gammopathy of undetermined significance
MRD	measurable residual disease
MVO_2	myocardial oxygen consumption
Nt-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OS	overall survival
PET	positron emission tomography
PFS	progression free survival
PIB	Pittsburgh compound B
PR	partial response
RI	retention index
ROC	receiver operating curve
RV	right ventricle
SAP	serum amyloid P
SUVR	standardized uptake value ratio
SVI	stroke volume index
TAPSE	tricuspid annular plane systolic excursion
TRM	treatment related mortality
T1	longitudinal relaxation time
T2	transverse relaxation time
VCd	bortezomib, cyclophosphamide, dexamethasone
VGPR	very good partial response

Introduction

Systemic immunoglobulin light chain (AL) amyloidosis is a rare disease caused by a, usually small, bone marrow plasma cell clone which produces free light chains with the ability to aggregate and form amyloid plaques. Amyloid deposition is systemic and can affect various organs such as the heart, kidney, liver, gastrointestinal tract, peripheral and autonomous nervous system. Patients can present with a wide range of symptoms depending on the type of organ involvement, these include oedema, shortness of breath, gastrointestinal symptoms, weight loss, skin changes, peripheral neuropathy and orthostatic hypotension. Symptoms are unspecific for amyloidosis, and more typical signs such as macroglossia, periorbital purpura and bilateral carpal tunnel syndrome are in fact relatively uncommon. Many clinical findings such as increased cardiac wall thickness, proteinuria, hepatomegaly and neuropathy can have various other causes. This requires for the physician to actively think of amyloidosis as a differential diagnosis in order to proceed with more directed investigations. Historically, the awareness of the diagnosis has been low, and the general perception was that of an untreatable disease with no chance of long-term survival for the patient. Furthermore, the lack of reliable methods for amyloid typing caused uncertainty regarding classification of the disease and the possibility of treatment.

Early diagnosis of AL amyloidosis is one of the most important factors for survival. Delay in diagnosis causes organ failure to progress, which limits treatment possibilities and the chance of organ recovery after treatment. With higher awareness of the disease and improved diagnostic methods, earlier diagnosis has been promoted. In combination with more effective treatments, the prognosis of patients is improving. Progress is also seen in ATTR (transthyretin amyloidosis), the other major amyloidosis subtype involving the heart, with the introduction of new treatments where there previously were no treatment possibilities. This has led to an increased awareness of amyloidosis among cardiologists and to more patients with heart symptoms being evaluated for amyloidosis in general, which likely has had a positive impact on the diagnosis of AL patients as well.

However, in a survey of 533 amyloidosis patients from 2015, 37.1% of patients reported that the diagnosis was delayed more than a year after the initial symptoms (1). And in a recently published European observational study, time from symptoms to the diagnosis of AL amyloidosis had not

improved significantly for patients starting treatment after compared to before 2010 (2). Early mortality in AL amyloidosis is high with approximately ¼ of patients dying within the first 6 months after diagnosis (3). A reduction in early mortality in the later years has been reported from highly specialized centres (3, 4) but not from more real-world conditions (2), suggesting that patients remain to be diagnosed in advanced disease stages. Hence, there is still an unmet need for earlier diagnosis, especially when it comes to cardiac AL amyloidosis, and improved treatment strategies for patients diagnosed with advanced disease.

This thesis sought to increase the knowledge of the epidemiology of AL amyloidosis, investigate new imaging methods for early diagnosis and prognostication in cardiac amyloidosis, and evaluate treatment options with focus on patients with cardiac involvement.

Background

Amyloid formation

There are more than 40 different proteins identified, with the ability of amyloid fibril formation (5), which is characterized by a cross-beta-sheet structure, and fluorescence when stained with Congo red (6). The origin of the amyloid forming proteins, as well as the organ affinity, varies widely. The pattern of distribution of amyloid deposits also differs between amyloidosis subtypes. In AL amyloidosis deposition is usually diffuse extracellular and arterial, as opposed to the nodular deposition more often seen in ATTR amyloidosis (7). Therapy can be directed against several stages in the amyloid formation process and differs markedly depending on the type of amyloidosis.

The origin of AL amyloidosis is a plasma cell clone producing amyloidogenic monoclonal immunoglobulin light chains. The plasma cell clone is usually small and indolent, although AL amyloidosis can also be associated with malignant disease (mainly myeloma or lymphoma) (8). When analysed with whole exome sequencing the plasma cells in AL amyloidosis do not present most of the driver mutations defined in myeloma, and generally display fewer mutations, but with an increase correlated with higher plasma cell count (9, 10). Studies have not been able to identify a common set of mutations for AL amyloidosis, instead there seems to be a greater clonal heterogeneity compared to myeloma.

Mutations in the variable domain of the light chain (IGVL) genes are frequent and can cause destabilization of the domain making the light chains prone to aggregation. Mutational hotspots are more frequent in lambda compared to kappa light chain genes (11). Specific IGVL gene mutations have been associated with systemic compared to localized AL amyloidosis, as well as with type and grade of organ involvement (12). For example, the mutation LV1-44 has been associated with heart, LV6-57 with kidney and KV1-33 with liver involvement.

Aggregation is partially dependent on the level of the precursor protein. But in some patients, low FLC levels can still be associated with advanced stage amyloidosis. It has been shown that in these patients, the location of the IGVL gene mutations, rather than the amount of the precursor protein determine the propensity for amyloid formation (13). Cryogenic electron microscopy studies have been able to localize mutational changes as well as post-

translational modifications such as disulphide bond and N-glycosylation in the fibril protein, and connect these to fibril morphology (14).

When analysing gene expression, there are differences between plasma cells in AL amyloidosis compared to plasma cells in myeloma or MGUS (monoclonal gammopathy of undetermined significance). Genes overexpressed in AL amyloidosis are related to for example chromatin organization and N-linked protein glycosylation (15). It has been shown that N-glycosylation of light chains is increased in AL amyloidosis (especially of kappa subtype) compared to other plasma cell diseases, and associated with the development of AL amyloidosis from MGUS (16). The N-glycosylation shows a pattern that differs from what is seen in non-amyloidogenic clonal light chains (17), suggesting that it plays a pathogenic role at least in a subset of AL patients.

In fibril formation, the amyloidogenic immunoglobulin light chains first aggregate into soluble oligomers/protofibrils, which then misfold and aggregate further into the cross-beta-sheet structure of amyloid fibrils (6). Interactions with the extracellular environment may cause proteolytic cleavage and binding of components such as glycosaminoglycans and collagen that facilitate aggregation (11). In vitro, factors such as high temperature and extreme pH values have been shown to destabilize proteins facilitating amyloid formation. The glycoprotein serum amyloid P (SAP) binds to amyloid fibrils independent of the origin protein, stabilizing the amyloid fibrils and preventing degradation. Apart from the type of IGVL gene mutations, the organ affinity can also be influenced by local conditions such as pH, presence of salts and interaction with various tissue constituents (18).

All amyloid fibrils have the ability to self-propagate through recruitment of more precursor proteins from the surroundings, referred to as “seeding”(11). This process proceeds slowly in the beginning and accelerates as the number of amyloid fibrils increases. If the amyloid burden is reduced, the self-replication rate decreases.

Epidemiology

AL amyloidosis was previously referred to as the most common type of systemic amyloidosis, and studies (19-21) have reported a higher incidence for AL than for ATTR and AA amyloidosis. However, a population-based autopsy study from Finland (22) showed that wild-type ATTR was present in the myocardium of 25% of subjects from 85 years of age. Furthermore, when screening patients with heart failure and preserved ejection fraction with bone scintigraphy, 13-18% has been found to have wild-type ATTR amyloidosis (23, 24), and 16% screened positive among patients undergoing aortic valve replacement (25). Thus, the incidence of wild-type ATTR has likely been underestimated and is probably higher than for AL amyloidosis.

The first published incidence number of AL amyloidosis is that from Kyle et al (19) who reported on the incidence of systemic AL amyloidosis in Olmsted County, Minnesota between 1950 and 1989. For residents in this region, almost all medical diagnoses were made at the Mayo Clinic and one more medical institute and were recorded in a centralized registry. Review of patient records with amyloidosis diagnosis in this registry, as well as autopsy reports resulted in 21 patients that fulfilled criteria set out for AL amyloidosis (typing of biopsy or autopsy material, or the presence of amyloid plus a monoclonal protein). The age- and sex-adjusted incidence was calculated to 8.9 (95% CI 5.1-12.8) per million person-years. The same authors published a similar incidence study from the same region during the time period 1990 to 2015 (26). 35 patients with AL amyloidosis were identified, and the age- and sex-adjusted incidence was calculated to 12 (95% CI 8-16) per million person-years. No significant change in the incidence was observed during the studied time period. When including the incidence reported in the previous study, there was a trend towards an increasing incidence, but without statistical significance. In the two studies, the reported median age at diagnosis of AL amyloidosis was 73.5 and 76 years respectively, and there was a male dominance with 62 and 54% males.

One recently published incidence report from Taiwan used their National Health Insurance Database, described as a population-based claims database, and identified all patients who received the international classification of diseases (ICD-10) code of amyloidosis (E85.4 “organ limited amyloidosis”, E85.8 “other amyloidosis” or E85.9 “amyloidosis unspecified”) and had an adjacent record of biopsy taken from a site possibly involved by AL amyloidosis (27). 841 cases were identified and the age-adjusted incidence was calculated to 5.26-6.55 cases per million person-years. A study from Sweden used similar methodology based on diagnose codes from the National Patient Register (28). The same ICD-10 codes as in the Taiwanese study were used, and inclusion also demanded one of the following 1) prescription of an anti-plasma cell therapy, 2) diagnosis made on a haematology or oncology clinic or 3) the specific code for AL amyloidosis E85.8A was used. The study identified 846 cases, and the age-adjusted incidence ranged from 5.4 to 6.8 per million person-years during the studied time period, with significant increase over time. However, in both of these studies, cases were not confirmed as having AL amyloidosis, and especially since there previously was no specific diagnose code for AL amyloidosis in the ICD system, there is a risk of misclassification. Other epidemiological studies in AL amyloidosis are not population-based or present merely an estimation of the incidence (20, 21, 29, 30).

Little is known about the incidence of AL amyloidosis in different ethnicities. In other plasma cell dyscrasias such as MGUS and myeloma, there are marked variations between ethnicities, with an increased incidence in African Americans and Hispanics, and a lowered incidence in Asians and Pacific Islanders compared to Whites (31, 32). In the incidence studies from Olmstead

County, almost all cases were Whites, which represented the composition of the studied population. The incidence number from the Taiwanese study was lower, which could reflect differences between ethnicities. In a report from Boston amyloidosis centre, ethnic minorities with AL amyloidosis were underrepresented, compared to what would be expected from the general population, especially the presence of Hispanics were unexpectedly low (33). However, this could also be influenced by disparities when it comes to referral to a specialized amyloidosis centre.

There are few studies of the prevalence of AL amyloidosis. One study based on cases from United States insurance claims data (not truly population-based) found an increase in the standardized prevalence from 20.1 cases per million in 2007 to 50.1 per million in 2015 (30). The previously described Swedish study (28) reported a significant increase in 5-year limited duration prevalence from 32 per million in 2011 to 47 per million in 2019. In a study of the global epidemiology of AL amyloidosis (34), estimations of the prevalence were performed based on previously published incidence and survival data. An increase in the estimated prevalence was found in all of the analysed countries. The estimated 5-year prevalence in 2018 for Sweden was 32.3 cases per million and 20-year prevalence was estimated to 56.7 per million.

Diagnosis

The presence of a monoclonal protein together with unexplained cardiac hypertrophy, proteinuria, hepatomegaly, peripheral neuropathy or hypotension should lead to the suspicion of AL amyloidosis. In around 90% of the cases, amyloid can be found in abdominal fat or bone marrow aspirate/biopsy (35). In cases where both fat and bone marrow are amyloid negative, and there is still a suspicion of AL amyloidosis, biopsy should be performed from the affected organ. Bone marrow sample is also indicated to evaluate the size of the plasma cell clone, which is a prognostic factor in AL amyloidosis (36). FISH (fluorescence in situ hybridization) analysis of bone marrow plasma cells can also provide prognostic information, which is described further on.

The beta-pleated-sheet configuration of amyloid causes the characteristic positive Congo red staining when viewed under polarized light, which is a requirement of amyloidosis diagnosis. According to the IMWG (International Myeloma Working Group) criteria (37), the diagnosis of AL amyloidosis requires all of the following:

1. Prescence of amyloid related systemic disease (cardiac, renal, hepatic, gastrointestinal or nervous system involvement)
2. Positive Congo red staining in any tissue
3. Evidence that the amyloid is light chain related
4. Evidence of a monoclonal plasma cell proliferative disorder (monoclonal protein in blood or urine, abnormal FLC ratio or clonal plasma cells in the bone marrow)

Accurate classification of the amyloid is crucial. Presence of a monoclonal protein together with unclassified amyloid in biopsy material is not enough, since MGUS is present in about 20% of patients with wild-type ATTR amyloidosis (38). Typing of the amyloid can be performed by immunohistochemistry, mass spectroscopy, immune-electron microscopy, western-blot or a combination of methods (39). In a study of 117 amyloidosis patients, immunohistochemistry performed by specialized pathologists was able to classify the amyloid in 94% of cases (40). Mass spectroscopy has high accuracy in detecting and classifying amyloidosis (41), the method also has the ability to detect peptide sequences from the mutated IGVL genes, thereby revealing the pathogenesis of the disease (42). Immuno-electron microscopy is used at some centres and can also characterize amyloid with high accuracy (43). The specialized amyloid laboratory in Uppsala uses western-blot in combination with immunohistochemistry, and if needed mass spectroscopy for amyloid typing. 84% of their samples could be typed with western-blot and immunohistochemistry, and the majority of cases not typed with this method were due to minimal amyloid deposits usually seen in ATTR (44).

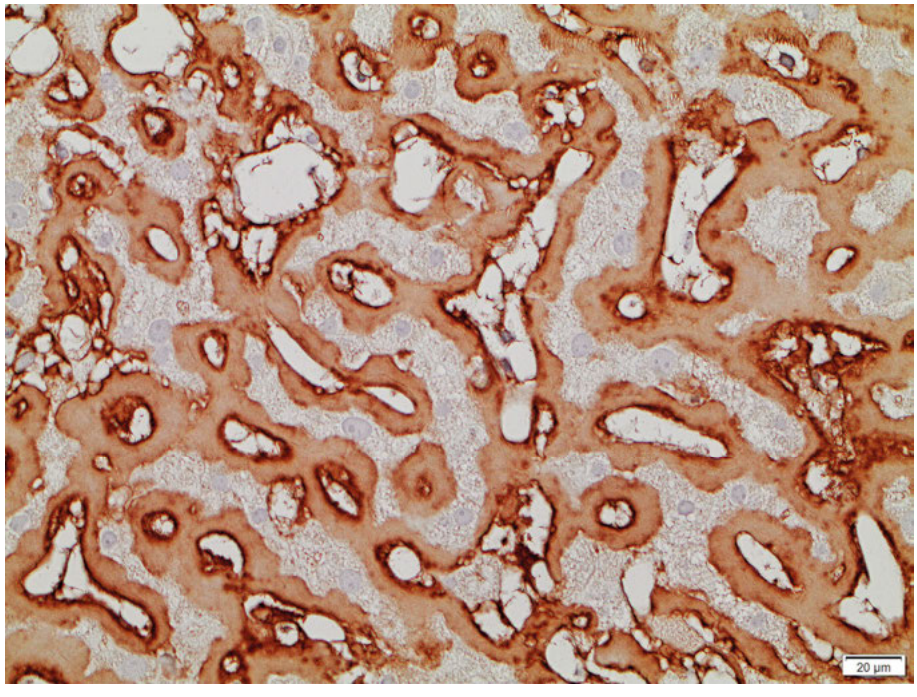

Figure 1. Liver biopsy with AL kappa amyloidosis. Pronounced amyloid deposition (in brown) is demonstrated with immunohistochemistry and a monoclonal antibody against AL kappa. Courtesy of Professor Per Westermark.

In patients with clinical suspicion of amyloidosis, serum and urine immunofixation together with serum FLC measurement can be used as a screening method for AL. In a study of 121 AL amyloidosis cases, the serum FLC ratio was pathologic in 76% of the cases, whereas serum and urine immunofixation together with FLC ratio captured 100% of AL cases (45).

Except from evaluation of the plasma cell clone, investigations are performed to evaluate the extent of organ involvement. Because of the increased risk of bleeding in amyloidosis patients, biopsies to determine organ involvement generally should be avoided, and non-invasive methods are recommended. The original consensus criteria published 2005 from the 10th International Symposium of Amyloidosis were established to define organ involvement (46). When assessing heart involvement, measurement of cardiac biomarkers (Nt-proBNP and troponins), as well as ECG (electrocardiogram) and echocardiography are indicated. Cardiac magnetic resonance imaging (CMR) or positron emission tomography (PET) with amyloid binding tracers can also be used in the evaluation of suspected amyloidosis. Elevated Nt-proBNP or troponins without other possible causes as well as typical imaging features on CMR or PET have been included as criteria for cardiac involvement in a newer consensus document (47).

Table 1. Criteria for organ involvement.

Organ involvement	Criterion (46, 47)
Heart	Mean wall thickness > 12 mm on echocardiography or Elevated Nt-proBNP or troponin without other cause or Typical features on CMR or amyloid specific PET
Kidney	24h-urine albumin > 0.5 g
Liver	Liver span > 15 cm or Alkaline phosphatase > 1.5 times the upper limit of normal
Gastrointestinal	Biopsy verification with symptoms
Nervous system	Symmetric sensory or motor peripheral neuropathy or Autonomous neuropathy
Lungs	Biopsy verification with symptoms Interstitial radiologic abnormalities

Cardiac imaging

ECG changes are common including low voltage (46%), pseudo infarct pattern (47%), criteria for left ventricular hypertrophy (16%) and atrial fibrillation (10%) (48). However, low voltage is reported to be a late finding in AL cardiac amyloidosis and is not useful for early detection of the disease (49).

Echocardiography is still the basis of cardiac assessment in amyloidosis. According to the original definitions of organ involvement (46), cardiac AL amyloidosis is considered evident if amyloid is detected and typed on any localization, and echocardiography shows a left ventricular wall thickness > 12 mm. Except from increased cardiac wall thickness, echocardiography typically shows diastolic dysfunction and in around half of the patients a "granular sparkling" pattern of the myocardium (50). Decreased ejection fraction is usually only seen in late stages of cardiac amyloidosis. Tissue doppler and speckle tracking imaging provides quantification of the motion and deformation of regional myocardium, and allows for measurement of longitudinal strain. Typically, in cardiac amyloidosis, deformation is reduced in basal and middle segments, while preserved in apical segments until late stages (51).

Endomyocardial biopsy is considered the gold standard for diagnosis of cardiac amyloidosis. However, the method is invasive and not considered indicated if amyloid is detected and classified elsewhere. A complication rate of up to 6% has been reported, involving for example arrhythmia, pneumothorax, focal neurological complications and perforation (52).

Except from echocardiography, CMR is a commonly used imaging method in cardiac amyloidosis. Traditionally, gadolinium contrast has been used showing late gadolinium enhancement with a distinct pattern from subendocardial to transmural as the disease progresses. More recently non-contrast CMR with T1 (longitudinal relaxation time) mapping has showed high accuracy in detecting cardiac amyloidosis (53, 54). Measurement of extracellular volume (ECV) with CMR provides quantification of the amyloid containing extracellular space; however, this method requires the administration of contrast agent. Compared to T1 mapping, ECV gives a more specific measurement of amyloid burden, as opposed to T1 mapping that is based on the signal from both the myocytes and the extracellular space (54).

Several PET-agents have been investigated in cardiac amyloidosis, the most studied are ^{11}C-PIB (Pittsburgh compound B), ^{18}F-florbetapir and ^{18}F-florbetaben, all of which have shown increased tracer-uptake in both AL and ATTR cardiac amyloidosis (55-57). These compounds are thioflavin-T derivates that binds to the beta-pleated structure of amyloid fibrils of any type, but with higher affinity for AL than for ATTR amyloidosis (58). ^{11}C-PIB was first developed to image beta-amyloid in Alzheimer's disease (59). Later several small studies have shown high accuracy of ^{11}C-PIB PET in detecting cardiac amyloidosis (55, 60-62).

Table 2. Previous ^{11}C-PIB PET studies in cardiac amyloidosis.

Author, year	No of subjects	Measure	Sensitivity	Specificity	Accuracy
Antoni, 2013 (55)	10	Visual	100%	100%	100%
Minamimoto, 2020 (60)	9	Visual	100%	100%	100%
Lee, 2015 (62)	22	SUVR>2.0	87%	100%	91%
Ezawa, 2018 (61)	15	Visual	92%	83%	89%

SUVR, standardized uptake value ratio.

Amyloid PET detects both AL and ATTR cardiac amyloidosis, but can possibly be used to differentiate between the two subtypes, since a sustained tracer uptake is seen in AL, as opposed to ATTR where increased uptake is seen early after tracer injection (56). This might be an advantage with PET compared to CMR in amyloid diagnostics.

Both CMR and PET have shown positivity for amyloid in a proportion of patients who do not fulfil the echocardiographic criteria for cardiac involvement (63, 64) and thus seems to be more sensitive methods to detect cardiac amyloidosis. Even among patients without elevation of Nt-proBNP, a substantial proportion has cardiac involvement according to ECV measurement and

amyloid PET uptake (63). As mentioned earlier, typical features of cardiac amyloidosis on CMR or PET can, according to recent guidelines be used to define cardiac involvement in extracardiac biopsy proven AL or ATTR amyloidosis (47).

When it comes to radio nuclear methods, SAP-scintigraphy can visualize AL amyloid in the spleen, liver and kidneys, but the method is not able to detect cardiac amyloid deposition (65, 66). Moreover, the method is not approved in all countries due to the need for human plasma in tracer production.

Radionuclide bone scintigraphy with technetium-labelled bisphosphonates has shown high sensitivity and specificity in detecting cardiac ATTR amyloidosis but the method is only able to visualize cardiac amyloid in a small proportion of patients with AL amyloidosis (67-69). As mentioned above, when investigating patients with unexplained cardiac hypertrophy, serum and urine immunofixation together with serum FLC is an effective screening method for AL amyloidosis. If a monoclonal protein is found, abdominal fat pad and bone marrow aspirate/biopsy is then the next investigational step. If no monoclonal protein is detected, AL amyloidosis is unlikely and ATTR should be suspected. Gillmore et al (70) have shown that a positive bone scintigraphy together with the absence of a monoclonal protein can safely be used to diagnose ATTR cardiac amyloidosis without the need of endomyocardial biopsy.

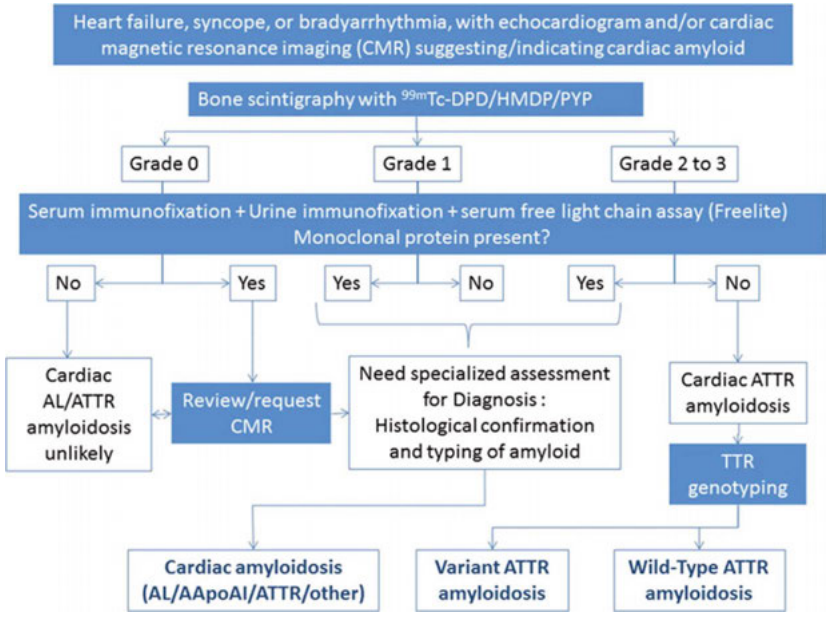

Figure 2. Algorithm for the diagnosis of cardiac amyloidosis, from Gillmore et al (70). Reproduced with permission from the publisher.

Effects on cardiac function

Cardiac dysfunction in AL amyloidosis is caused both by the disruption of tissue architecture by amyloid deposition and by the toxic effects of mainly the prefibrillar forms of the amyloidogenic light chains (oligomers). Amyloid deposition leads to expansion of the extracellular space, increased cardiac wall thickness and stiffening of the heart without compensatory dilatation. This results in a restrictive and diastolic dysfunction with elevated filling pressures and reduced stroke volume which involves both ventricles. In severe stages, the systolic function is also decreased (50). Amyloid deposition also occurs in the atria causing reduced contractility (71), as well as in the valves and perivascularly.

It has been shown that with the same degree of increased cardiac wall thickness, AL patients have more pronounced cardiac dysfunction and shorter survival than ATTR patients (72). Animal studies have shown that infused amyloidogenic light chains cause direct toxicity to zebra fish cardiomyocytes (73), and reduces the motility of the nematode C. elegans, which can be used as a model of the vertebrate heart (74). There is evidence that the amyloidogenic light chains cause impairment of cardiomyocyte metabolism, activation of apoptosis and increased oxidant stress. This causes decrease in cardiomyocyte contractility and relaxation (75-77), effects that are mediated through p38 MAPK (mitogen-activated protein kinase) signalling (78, 79). The p38 MAPK activation leads to Nt-proBNP release, which in AL amyloidosis is caused both by the cardiotoxic effect of the light chains and by the general mechanisms leading till Nt-proBNP release in heart failure (80).

Another factor influencing cardiac function might be myocardial oedema, which by CMR T2 (transverse relaxation time) mapping and histology has been shown to be increased in cardiac amyloidosis, more so in AL than in ATTR. Increased myocardial oedema on T2 mapping has also been associated with inferior survival in AL patients (81).

Angina and “infarction-like” conditions are prevalent in cardiac amyloidosis, and in a study of specimens from AL patients, 74% were found to have histological signs of myocardial ischemia (82). There is evidence of microvascular dysfunction which can be caused by endothelial dysfunction due to toxic effects of the light chains or by small vessel involvement of amyloidosis (83).

Assessment of cardiac function by PET

Apart from detection of cardiac amyloidosis, PET can be used to assess different aspects of cardiac function, using for example the tracer ^{11}C-acetate. Acetate is used in the mitochondria to convert nutrients and oxygen into ATP (adenosine triphosphate). Carbon dioxide is the main metabolite of acetate

oxidation, and leaves the tissue in direct proportion to the carbon oxidation, and is then finally exhaled. That is why radiolabelled acetate can be used with PET to measure oxidative metabolism. The high extraction and uptake into myocytes also make it suitable for measuring myocardial blood flow (MBF). The influx phase of ^{11}C-acetate is used to measure MBF and the efflux phase to measure MVO_2 (myocardial oxygen consumption). Cardiac output (CO) can be quantified with high accuracy and forward stroke volume calculated (CO/heart rate). Furthermore, left ventricular (LV) volumes, ejection fraction, LV mass and septal wall thickness (IVS) can be measured. Efficiency of the myocardium (MEE) is defined as the ratio of energetic output and the energy consumed, and can be calculated from ^{11}C-acetate PET (84). In the diagnosis of ischemic heart disease, ^{11}C-acetate PET can be used to measure perfusion and metabolism simultaneously, but due to the relatively long half-life of ^{11}C-acetate the use is limited when both rest and stress measures must be performed in the same session.

In cardiac amyloidosis, PET-studies have shown reduced MBF (85, 86), which is assumed to be caused by the obstruction of blood flow from the amyloid infiltration, or possibly from amyloid involving the blood vessel walls. Elevated ratio of right and left ventricular (RV/LV) MBF has been shown to be associated with increased pulmonary pressure and to have prognostic implications in AL and ATTR cardiac amyloidosis (87). A value of RV/LV MBF > 0.56 was shown to predict inferior survival, and was mainly driven by increased RV MBF, which could be related to an increased demand due to elevated RV afterload.

In one previous ^{11}C-acetate PET study of MEE in cardiac amyloidosis, MVO_2 was relatively unchanged, whereas MEE was reduced, indicating a poor energetic efficiency but without any severe effect on the oxidative metabolism (85).

Treatment

Until recently, there were no treatment regimens approved by medical agencies for AL amyloidosis. The daratumumab-VCd (bortezomib, cyclophosphamide, dexamethasone) combination was the first treatment to be approved in 2021, based on results of the ANDROMEDA study (88). The study was a randomized trial were patients received six 4-week cycles of VCd with or without the addition of daratumumab. The daratumumab group also continued to receive daratumumab for up to 24 cycles in total. The study showed a significantly higher rate of hematologic complete response (CR) in the daratumumab group (53.5 vs 18.1%), and also a significantly higher rate of organ responses. The study did not include patients with advanced stage cardiac involvement.

Otherwise, therapies are mainly adopted from what is used in myeloma. Randomized studies are rare, and treatment recommendations are mostly based on small phase 2 studies. Another issue has been incoherence in the reporting of results from clinical trials in AL amyloidosis. Since early mortality is high, response numbers are largely affected by whether results are reported as "intention-to-treat" or not, a problem that has been addressed in a publication by Comenzo et al (89). Furthermore, patients with advanced stage cardiac involvement, the patient group most in need of improved therapeutic options, are often excluded from clinical trials.

All treatments used in clinical practice today are directed towards the plasma cell clone, with the aim of eliminating the amyloidogenic light chains from the circulation, thereby preventing further amyloid formation and enabling reduction of existing organ deposition. There is still no evidence that the disease is curable, and patients need to be followed lifelong.

High dose melphalan

High dose melphalan and autologous stem cell transplantation (HDM/ASCT) has been performed since the 1990s and is still considered standard of care for eligible patients at many centres. There is only one randomized study comparing high dose melphalan to conventional chemotherapy (90). In this study, 100 patients were randomized to receive either HDM/ASCT or standard dose melphalan together with high dose dexamethasone. However, in the group assigned to receive HDM/ASCT, only 37 patients came to treatment (10 patients died, 1 declined treatment and 2 did not have enough stem cells). Out of these 37 patients, 9 died within 100 days from treatment, that is, treatment related mortality (TRM) was 24%. In an "intention-to-treat" analysis, the median overall survival (OS) was significantly longer in the group assigned to receive standard dose melphalan compared to high dose (56.9 vs 22.2 months), and no significant difference in response rates was seen between the groups either. However, no patient selection was made in the study, and high-risk patients were present in both arms (21 of the patients in the high dose melphalan group). When divided into high-risk and low-risk disease, there was no significant difference in OS between the standard dose and high dose melphalan groups.

Since then, it has been shown that patient selection can improve the results of HDM/ASCT, and a risk-adapted approach is now being used when assigning treatment for patients. In the later years, large amyloidosis centres have reported good long-term results with HDM/ASCT, with median OS between 7.3 and 10.4 years and hematologic CR rates of around 40-50% (91-93). The reported TRM is reduced from 7.4-8.7% to 1.1-3.3% in the later years. In the largest studied patient population including 1536 patients from the Centre for International Blood and Marrow Transplant Research registry, TRM was 20% in 1995-2000, 11% in 2001-2006 and 5% in 2007-2012 (94). 5-year survival

rate increased from 55% to 61% and 77% in the latest time period. They also reported superior survival in centres that performed more than four transplantations per year for AL amyloidosis.

Table 3. Previous studies on high dose chemotherapy in AL amyloidosis.

Author, year	Centre	Time-period	No of pts	TRM	CR rate	OS
Sharpley, 2019 (91)	UK	1994-2018	264	8.7% (18.8→1.1%)	52%	7.3 y
Sidiqi, 2018 (92)	Mayo Clinic	1996-2016	672	7.4% (14.5→2.4%)	40%	10.2 y
Gustine, 2022 (93)	Boston	1994-2021	648	8% (11.8→3.3%)	39%	7.6 y
D´Souza, 2015 (94)	Interna-tional	1995-2012	1536	20→5%	30-37% (2001-2012)	55-77% 5y OS

TRM, treatment related mortality. CR, complete response. OS, overall survival.

Selection criteria for HDM/ASCT

The proportion of patients treated with high dose therapy has varied widely between centres, with around 30% reported from the United States (3) compared to 5-6% from European centres (2, 91), suggesting that varying selection criteria have been used. During the later years, a decreasing trend has been observed in the frequency of HDM/ASCT, probably due to stricter selection of patients for treatment (92).

Cardiac involvement is the main risk factor for treatment related mortality. Nt-proBNP > 5000 pg/mL and Troponin T > 0.06 ng/mL have been identified as risk factors for early mortality after HDM/ASCT. It has been suggested that patients with these risk factors should be excluded from high dose treatment (95). In 2022, guidelines for HDM/ASCT in AL amyloidosis were published by an International Society of Amyloidosis/European Haematology Association working group, including the mentioned cardiac biomarker levels as well as other parameters (96). The proposed eligibility criteria for high dose therapy were as follows:

- Age <70 years (>70 years may be discussed)
- At least one major organ involvement
- LV ejection fraction ≥40%, NYHA class <III
- Oxygen saturation ≥95%, diffusing capacity >50%
- Supine systolic blood pressure ≥90 mmHg
- ECOG performance status ≤2 unless limited by peripheral neuropathy

- Direct bilirubin <20 mg/L
- Nt-proBNP <5000 pg/mL
- Troponin T <0.06 ng/mL, troponin I <0.1 ng/mL or highly sensitive troponin T <75 ng/L
- eGFR >30 mL/min/1.73 m^2 if not on dialysis (otherwise the dose of melphalan should be reduced)
- No symptomatic arrhythmias or pleural effusions
- No uncompensated heart failure
- No factor X deficiency (<25% or active bleeding)
- No extensive gastrointestinal involvement with risk of bleeding

The role of induction therapy

The use of induction therapy before HDM/ASCT has increased over time (3, 91, 92), and in retrospective studies induction therapy has been associated with higher CR rate and longer OS after HDM/ASCT (93, 97, 98). One of the studies could not show an advantage with induction therapy in patients with bone marrow plasma cells (BMPC) less than 10%, however another retrospective analysis showed benefit with induction therapy independent of the amount of BMPC (93). There is one randomized study including 56 patients comparing bortezomib induction to no induction (99). With all subjects remaining on study at 12 months, the CR rate was significantly higher with bortezomib induction (67.9% vs 35.7%). Bortezomib based induction therapy can also make around 30% of patients initially considered ineligible for HDM/ASCT possible to treat (86).

Induction therapy might serve as a "test" of how well the patient tolerate treatment, and if toxicity or disease progression occur during induction therapy the patient may never proceed to high dose therapy. This might influence study results in advantage of induction therapy if "intention-to-treat" results are not reported.

Deferred HDM/ASCT to progression

Results are diverse regarding deferred HDM/ASCT to progression. A retrospective study by Manwani et al (100) showed significantly shorter OS from the time of ASCT when HDM/ASCT was deferred to progression compared to as consolidation. However, these results may be biased by the fact that having disease progression itself infers worse prognosis. On the other hand, Venner et al showed no significant difference in OS (not if measured from the time of ASCT or from diagnosis) with HDM/ASCT performed at progression compared to upfront (101).

HDM/ASCT in comparison to modern conventional treatment

There are no randomized studies comparing high dose to conventional chemotherapy in the era of modern treatment. With the recently approved

combination daratumumab-VCd in newly diagnosed AL amyloidosis, response rates are similar to what has been reported after HDM/ASCT (88). After 6 cycles of daratumumab-VCd, the hematologic CR rate was 53.3% compared to around 40-50% after HDM/ASCT. Organ response rates were 41.5% for cardiac and 53.0% for renal response with daratumumab-VCd. The reported rate of renal response with HDM/ASCT is between 31-32% (94) to 76% and 61% for cardiac response (93). A median duration of response of 12.3 years has been reported in patients achieving CR after HDM/ASCT (93), whereas the duration of response with daratumumab-VCd therapy is not yet evaluated. There are of course issues with comparing results between studies. The study populations differ and patients receiving high dose therapy is generally a highly selected group. The reporting of hematologic and organ responses from the retrospective studies depends on the methods and criteria used during that time-period. Results are also affected by whether results are reported for the "intention-to-treat" population or not.

The long overall and progression free survival reported after HDM/ASCT is the main advantage with HDM/ASCT, and it is not yet known whether the same long-term results can be obtained with daratumumab-VCd treatment. Treatment related mortality and morbidity is still an issue with HDM/ASCT, even though the TRM is markedly reduced over time it is still a few percent and higher than the around 0.5% (102, 103) observed in multiple myeloma. Based on that, the current recommendation is to refrain from high dose therapy in first-line treatment in patients achieving CR with induction therapy (96).

Treatment in advanced cardiac stage

Around 17% of AL amyloidosis patients have advanced (stage IIIb) cardiac involvement at diagnosis (2). For this group, median survival is short (4-6 months) (104-106) with only a small increase to 9 months in a recent report where 74% of patients received bortezomib or daratumumab based first-line therapy (107). Early mortality is high at around 40% within 3 months from diagnosis and has not decreased over time according to a recent European report (2).

Rapid and deep hematologic response is particularly important in this group, and can increase survival (104, 105, 107). Hematologic response of at least VGPR (very good partial response) at 1 month and an early cardiac response within 3 months is associated with prolonged survival (104, 107). However, the tolerability of treatments is of course an issue. For example, there are reports of cardiac toxicity from dexamethasone as well as bortezomib, and it is suggested that the timing and dosing of these drugs should be adapted (108, 109).

Patients with advanced cardiac stage are excluded from treatment with HDM/ASCT according to the guidelines described above, due to the high risk of treatment related mortality. In the ANDROMEDA study comparing

daratumumab-VCd to VCd, patients with advanced cardiac involvement (Nt-proBNP > 8500 ng/L or NYHA class IIIb/IV) were not included (88). 36% of patients in each arm were in stage III (Nt-proBNP ≥ 1800 ng/L and troponin T ≥ 0.025 ng/mL), these patients also benefitted from daratumumab-VCd. However, early mortality (within 60 days of starting treatment) was equal in the two study groups, indicating that the addition of daratumumab could not overcome the risk of early death.

The daratumumab-VCd combination has been evaluated retrospectively in 19 patients with stage IIIb cardiac disease (110). The starting dose of bortezomib was reduced in 50% of patients and omitted in one, dexamethasone was reduced to 10-20 mg/week while full dose cyclophosphamide and daratumumab was given from start. There were 3 deaths within 3 months (15.8%) which is better than the around 40% previously reported in stage IIIb patients. The authors stated that there were no treatment related deaths. However, it might be difficult to specify whether cardiac deaths are due to toxicity or not. Another retrospective study in stage IIIb patients has showed significantly higher hematologic and cardiac response rates, as well as prolonged survival, when daratumumab was included in first-line therapy (111).

Antibodies directed against the amyloid itself, and not the plasma cell clone, is an attractive approach in advanced cardiac involvement, with the hope of achieving a faster organ response. CAEL-101 is a monoclonal antibody directed towards amyloid proteins present in both kappa and lambda amyloid fibrils (112). A phase 1A/B study in 27 relapsed AL patients showed 67% organ responses, which were seen at in median 3 weeks from start of therapy. Phase 3 studies are now ongoing in stage IIIa and b patients in combination with standard of care plasma cell directed therapy. Another amyloid directed antibody under investigation is birtamimab that binds to an epitope of misfolded kappa and lambda light chains. The phase 3 VITAL study was closed early due to failure to meet endpoints in an interim analysis. However, in a post-hoc analysis of patients with Mayo stage IV disease, there was a significant improvement in survival at 9 months (113). A randomized study in stage IV patients is currently ongoing.

Prognosis

Cardiac biomarkers and staging systems

Cardiac involvement is the most important prognostic factor, and the cardiac biomarkers Nt-proBNP and troponins are the basis of prognostic systems used in AL amyloidosis. The Mayo Clinic staging system from 2004 used the thresholds Nt-proBNP 332 pg/mL, troponin T 0.035 ng/mL or troponin I 0.1 ng/mL (114). Elevation of both Nt-proBNP and troponin gave Mayo stage III,

one elevated stage II and none elevated stage I. Median survival for the groups was 4.1, 11.1 and 27.2 months respectively.

A revised Mayo staging system was published in 2012 with adjusted thresholds for Nt-proBNP (1800 pg/mL) and troponin T (0.025 ng/mL), and the inclusion of dFLC (difference between involved and uninvolved free light chain) with the threshold 180 mg/L (115). The new model yielded four different stages with scores 0-3 on these parameters, with median survival from diagnosis of 94.1, 40.3, 14 and 5.8 months respectively. This staging system was also validated using high sensitive troponin T measurement (116).

In a European collaboration study of 346 patients with 2004 Mayo stage III disease, Nt-proBNP > 8500 pg/mL and systolic blood pressure < 100 mmHg were identified as independent risk factors associated with inferior survival, suggesting that these parameters could be used to further risk stratify patients in Mayo stage III (117). In patients with both of these risk factors present, median OS was only 3 months, and with one of the risk factors present median OS was 6 months. In patients with either Nt-proBNP > 8500 pg/mL or systolic blood pressure < 100 mmHg, achieving hematologic CR was associated with improved survival, whereas achieving partial response (PR) did not lead to better survival.

In a retrospective European study of 230 patients treated upfront with VCd published in 2015 (106), Mayo stage III patients were sub-grouped into stage IIIa with Nt-proBNP < 8500 pg/mL and stage IIIb with Nt-proBNP ≥ 8500 pg/mL. Stage IIIb was the only independent risk factor for inferior survival.

In a comparison of the different staging systems Mayo 2004, Mayo 2012 and European 2015, the European system best predicted early mortality (at 1 year) (118). Mayo 2012, in which assessment of the plasma cell clone is included, outperformed the other systems regarding more long-term survival (at 3 years).

Table 4. Staging systems in AL amyloidosis.

Prognostic model	Measure	Stage	
Mayo 2004 with European modification	**1) Troponin** TnT≥0.035 ng/mL or TnI≥0.1 ng/mL or Hs TnT≥50 ng/L **2) Nt-proBNP** Nt-proBNP≥332 pg/mL or BNP≥81 ng/L	Stage I Stage II Stage IIIa Stage IIIb	No risk factors 1 risk factor 2 risk factors and Nt-proBNP<8500 pg/mL or BNP<700 pg/mL 2 risk factors and Nt-proBNP≥8500 pg/mL or BNP≥700 pg/mL
Mayo 2012	**1) Troponin** TnT≥0.025 ng/mL or Hs TnT≥40 ng/L **2) Nt-proBNP** Nt-proBNP≥1800 pg/mL or BNP≥400 pg/mL **3) dFLC**≥180 mg/L	Stage I Stage II Stage III Stage IV	No risk factors 1 risk factor 2 risk factors 3 risk factors

Plasma cell clone, FLC levels and cytogenetic abnormalities

Higher amount of bone marrow plasma cells and higher dFLC have been identified as negative prognostic factors in AL amyloidosis (36, 119). In 730 patients followed at the Mayo Clinic, the type of involved light chain, lambda or kappa, did not affect survival, but the presence of a heavy chain paraprotein was associated with a slightly better prognosis (119). Another study however reported shorter progression free and overall survival in lambda light chain amyloidosis compared to kappa, in patients treated with autologous stem cell transplantation (120).

Patients with low dFLC (< 50 mg/L), constituting around 15% of AL patients, have less often and less advanced cardiac involvement, whereas renal involvement is more common and more severe in this group (120-122). Overall survival is better in patients with low dFLC, who also have a survival benefit among patients within the same Mayo stage group. Patients with low dFLC (at least 20 mg/L) at diagnosis who achieve dFLC <10 mg/L after

treatment have longer overall and renal survival, suggesting that this should be the treatment goal in this patient group.

The most prevalent cytogenetic aberration in AL amyloidosis is translocation (11;14), present in around 50% of AL patients (123, 124). In patients treated with bortezomib first-line, t(11;14) has been associated with inferior prognosis (124-126). However, when treated with high dose melphalan, outcome is similar or better in patients with t(11;14) (127, 128). In a recent retrospective study including patients treated between 2016-2021, presence of t(11;14) was associated with higher frequency of swich to second-line therapy within one year (129). However, no effect on overall survival was seen, probably due to the possibility of receiving effective second-line treatment. The presence of t(11;14) is associated with sensitivity to the BCL2-inhibitor venetoclax, which has shown high efficacy in previously treated AL patients with t(11;14) (130). With daratumumab-VCd treatment, patients with t(11;14) had the same benefit of the addition of daratumumab as the whole daratumumab group (131).

Gain 1q21 is present in 20-30% of AL patients, and is overrepresented in patients with co-existing myeloma (123). Gain 1q21 has been associated with worse survival in patients treated with low dose melphalan first-line (132), but had no significant prognostic impact in a cohort treated with high dose melphalan (127).

The myeloma high-risk aberrations t(4;14), t(14;16) and del(17p) are uncommon in AL amyloidosis, around 2-3% each. These aberrations have been associated with inferior prognosis in patients treated with high dose melphalan, but not in patients treated with bortezomib (126, 127).

Cardiac function parameters

The degree of cardiac involvement at diagnosis is the major determinant of survival in AL amyloidosis. Even elevated Nt-proBNP or cardiac involvement detected by CMR, in patients with normal echocardiogram, are shown to be prognostic for survival (64).

Except from clinical (NYHA-class) and biochemical (Nt-proBNP, troponins) parameters, there are several echocardiographic and CMR measures that have been associated with inferior survival. Impaired longitudinal function measured with longitudinal strain (LS) is an early echocardiographic sign of cardiac amyloidosis. Several studies have shown independently prognostic value of LS in multivariable analysis involving cardiac biomarkers (133-137). Also, right ventricular dysfunction, typically assessed by TAPSE (tricuspid annular plane systolic excursion) is associated with poor prognosis in cardiac amyloidosis (138, 139). Other prognostic parameters are indexed stroke volume (SVI) and myocardial contraction fraction (MCF) calculated as LV stroke volume divided by LV myocardial volume. Both SVI and MCF are shown to be prognostic independent of cardiac biomarkers and MCF is highly correlated

to LS (136, 139, 140). According to a study by Milani et al, SVI, MCF and LS had similar prognostic value, and the authors suggested that SVI is used in clinical practice because it is routinely and easily assessed (136).

Treatment response

Hematologic response criteria and goal of treatment

The original response criteria (46) were updated in 2012 and four levels of hematologic response were defined, CR (negative serum and urine immunofixation and normal FLC ratio), VGPR (dFLC < 40 mg/L), PR (dFLC decrease > 50%) and no response (141). The level of FLC response is directly associated with survival, and correlate better with survival than monoclonal protein response in patients having intact immunoglobulins (142, 143). The absolute level of dFLC was a stronger predictor of survival than the percentage of FLC reduction, which is why the new response category VGPR with dFLC < 40 mg/L was established (141).

Studies have suggested a more stringent definition of CR, since both involved FLC (iFLC) ≤ 20 mg/L or below upper limit of normal (144, 145) and dFLC < 10 mg/L (146, 147) have performed better at predicting survival than the FLC ratio. However, not all studies have confirmed this finding (148). Recently published guidelines recommend CR with iFLC ≤ 20 mg/L or dFLC < 10 mg/L to be the goal of treatment (149). In patients with advanced cardiac stage (IIIb), achieving a rapid both hematologic and cardiac response is of special importance. Achieving VGPR within 1 month and cardiac response within 3 months is associated with superior survival and could be proposed as a goal of treatment (104, 107).

Assessment of MRD (measurable residual disease) by flow cytometry is established in myeloma and has been studied in AL amyloidosis. Retrospective studies have shown that undetectable bone marrow clonal plasma cells by flow cytometry (different techniques with varying sensitivity have been used) is associated with longer PFS, but without significant difference regarding OS (150-152). MRD by bone marrow flow cytometry could underappreciate disease because of varying presence of clonal plasma cells depending on the sample site. A recent study reported that, among 33 patients who were in CR and MRD negative using six-color flow cytometry (not next generation flow cytometry), four patients (12%) were positive by blood mass spectrometry (153). Further studies are needed to determine the value of this technique.

Evaluation of cardiac response

In the original organ response criteria published in 2005, cardiac response was defined as IVS decrease by 2 mm, 20% improvement in ejection fraction or

improvement by two NYHA classes (without increase in diuretic use), measures that are insensitive and observer dependent. Significant changes in Nt-proBNP are strongly associated with survival, and a new definition of cardiac response was established in 2012, with Nt-proBNP response defined as > 30% and > 300 pg/mL decrease if baseline Nt-proBNP was ≥ 650 pg/mL (141). Nt-proBNP can be used early (3 months after treatment initiation) to assess cardiac response. However, its use is limited in patients with renal failure since the level of Nt-proBNP is affected by the glomerular filtration rate, and it is also sensitive to temporary changes in fluid balance. In patients receiving IMiD (immunomodulatory drug) treatment, rises in Nt-proBNP is observed despite hematologic response, however, in this situation Nt-proBNP increase is still associated with worse outcome.

Further grading of cardiac response has been suggested by Muchtar et al, who proposed four levels of response with significantly differentiated survival rates: 1) cardiac CR, nadir Nt-proBNP ≤ 350 pg/mL, 2) cardiac VGPR, > 60% reduction in Nt-proBNP but not meeting cardiac CR definition, 3) cardiac PR, 31-60% reduction in Nt-proBNP and 4) non-responder, ≤ 30% reduction in Nt-proBNP (145, 154). The graded cardiac response performed better at predicting survival than the two-level response from one year after start of treatment. Median time to at least cardiac PR was 9.4 months (IQR 4.7–15.9).

In general, a complete hematologic response leads to the best outcome. However, the level of hematologic response at which organ response occur can vary between patients. The use of a combined hematologic and organ response score has been suggested, in order to better assess the overall response for the individual patient (155).

When it comes to imaging parameters, improvement in LS after treatment is associated with longer overall survival, and studies indicate superior prognostic performance compared to Nt-proBNP. It has been suggested that LS is incorporated in the staging system and also in the response assessment criteria in AL amyloidosis (134, 156). Reduction in ECV measured with CMR has also been associated with improved outcome in AL amyloidosis (157, 158).

Aims of the thesis

The overall aims of the thesis were to increase the knowledge about the epidemiology of AL amyloidosis, to study imaging methods for early diagnosis and prognosis assessment in cardiac AL amyloidosis, and to evaluate the long-term results of high dose chemotherapy in AL amyloidosis with focus on patients with cardiac involvement.

The use of high dose chemotherapy in AL amyloidosis is debated mainly because of the high mortality and morbidity that has been associated with the treatment. Studies from specialized amyloidosis centres have shown a reduction in the treatment related mortality over time, and superior results in centres performing > 4 high dose treatments per year. In **paper I** we aimed to evaluate the long-term results of all patients treated with high dose therapy for AL amyloidosis in Sweden during the first 15 years after the treatment was introduced. We sought to compare results from our Swedish conditions, where this treatment is performed in a decentralized setting, to the outcomes reported from the large amyloidosis centres regarding response, survival and treatment related mortality. We specifically wanted to evaluate results in patients with cardiac involvement, who have the highest risk of treatment related mortality, and analyse whether mortality has changed over time.

Cardiac involvement is the major determinant of prognosis in AL amyloidosis, and when diagnosed in advanced stages, prognosis is dismal. Echocardiography is the most used imaging method for diagnosis of cardiac amyloidosis, but many of the findings on echocardiography are unspecific for cardiac amyloidosis and occur late in the disease process. Previous pilot-studies have shown that PET with the amyloid binding tracer ^{11}C-PIB (initially developed for the diagnosis of Alzheimer's disease) can detect cardiac amyloidosis. **Paper II** aimed at determining the sensitivity and specificity of ^{11}C-PIB PET in detecting cardiac amyloidosis and evaluate differences in uptake in AL and ATTR amyloidosis. We also wanted to examine whether ^{11}C-PIB PET could detect cardiac amyloidosis in a group of patients without demonstrated heart involvement according to standard criteria, that is, if PET was able to detect cardiac amyloidosis earlier than echocardiography.

Since the degree of cardiac involvement is the most important prognostic factor, staging systems in AL amyloidosis are based on the level of cardiac biomarkers, mainly Nt-proBNP. However, the level of Nt-proBNP is not specific for the degree of cardiac involvement, it is also influenced by the

glomerular filtration and fluid balance, and often increases with IMiD treatment. Several cardiac function parameters have been investigated as prognostic markers in AL amyloidosis, such as longitudinal strain, stroke volume and myocardial contraction fraction. In **paper III** we wanted to examine the prognostic value of myocardial external efficiency from ^{11}C-acetate PET, a measure that incorporates oxygen consumption as well as mechanical parameters. Since oxygen metabolism could possibly be altered in cardiac amyloidosis, we hypothesized that the prognostic power would be increased compared to parameters based only on mechanical work.

There are few population-based epidemiological studies in AL amyloidosis. Many of the reports on the incidence and prevalence of AL amyloidosis are based on estimations, and the studies with verified cases include only a small number of patients. Survival data mainly come from large amyloidosis centres, where an improvement is seen over time. In **paper IV** we sought to determine the incidence, prevalence and survival of AL amyloidosis in Sweden, and evaluate whether the improvements seen regarding survival also applies to our conditions. The aim was also to evaluate whether the incidence and prevalence has changed during the last two decades, considering the increased awareness and survival of the disease. We also wanted to evaluate factors influencing overall and early mortality, such as cardiac involvement, and whether early mortality has changed over time.

Patients and methods

Paper I

We retrospectively collected data on all patients treated with HDM/ASCT in Sweden from 1994 when treatment was introduced until 2009. Patients were identified from registries at the eight different centres in Sweden were HDM/ASCT was performed. Patients with symptomatic myeloma (defined as myeloma diagnosis with CRAB criteria) or lymphoma were excluded. Data was retrieved from the time of diagnosis, at admission for HDM/ASCT, at 3 months, 6 months, 1 year and 2 years after HDM/ASCT, at best response and at progression. Follow-up was ended in April 2014. Response, treatment related mortality and overall survival were analysed, as well as factors influencing survival. The original consensus criteria from 2005 (46) were used to define organ involvement, response and progression. Changes in treatment related mortality between the earlier part of the studied period and the later were examined. Survival was analysed using Kaplan-Meier method, and differences between survival curves were measured with the log-rank test. The chi square test was used to evaluate differences in categorical values.

Paper II

36 patients with known cardiac amyloidosis (CA) were enrolled in the first part of the study, 15 patients with AL and 21 with ATTR amyloidosis, as well as two control groups consisting of healthy volunteers (n = 8) and patients with non-amyloid cardiac hypertrophy (n = 7). Subjects were examined with ^{11}C-PIB PET and echocardiography to establish the sensitivity and specificity of ^{11}C-PIB PET for the diagnosis of CA, and the optimal cut-off values for the two semi-quantitative measures SUVR (standardized uptake value ratio) and RI (retention index). We then applied these cut-off values prospectively to a group of patients with systemic amyloidosis (5 AL and 6 hereditary ATTR) without increased cardiac wall thickness.

The CA patients were diagnosed either by endomyocardial biopsy (n = 24) or by echocardiography showing hypertrophy together with amyloid detected on abdominal fat pad biopsy (n = 11), one of the AL patients had a positive fat pad biopsy and typical CMR findings for CA, even though echocardiography did not show increased wall thickness.

The majority of AL patients (12 out of 15) had received plasma cell directed therapy before study inclusion. Among the ATTR patients, 16 had wild-type and 5 hereditary ATTR, out of these 3 had the Danish Leu111Met mutation and 2 had the Swedish His88Arg mutation. The hypertrophic control group consisted of 4 patients with idiopathic hypertrophic cardiomyopathy and 3 with hypertrophy caused by hypertension.

All subjects were examined with ^{11}C-PIB PET and echocardiography, which were performed at two sites (Uppsala, Sweden and Aarhus, Denmark). PET/CT was performed according to identical protocols at the two sites, after ^{11}C-PIB injection a dynamic scan was performed during 35 minutes. All PET examinations were evaluated by two different observers blinded to the diagnosis of the subject, both by visual inspection and by the two semi-quantitative measures SUVR and RI, with good agreement between the readers. Regions of interest were drawn in the left atrial blood pool, and in the left ventricular wall, from which time-activity curves were created. Summed images from 10-20 minutes after ^{11}C-PIB injection were used to calculate the myocardium/blood SUVR, and for RI the mean tissue concentration between 10-20 minutes was divided by the integral of the blood time-activity curve from 0-15 minutes after ^{11}C-PIB injection.

ROC (receiver operating characteristic) curves were used to determine the cut-off values of SUVR and RI that discriminated CA from controls with the highest sensitivity and specificity. Spearman rank correlation or ordinal logistic regression was used to evaluate correlations between PET measures and clinical/echocardiography parameters.

Paper III

The study included 48 subjects with both AL (n=23) and ATTR (n = 25) cardiac amyloidosis as well as 20 controls (14 healthy volunteers and 6 with non-amyloid hypertrophic cardiomyopathy). ATTR patients comprised 18 wild-type and 7 hereditary ATTR, 4 with the Leu111Met mutation, 2 with the His88Arg mutation and one patient with unknown type of mutation.

The CA patients were diagnosed with endomyocardial biopsy (33 patients) or by abdominal fat pad biopsy together with echocardiography or CMR (15 patients). Hypertrophic controls consisted of 3 patients with hypertensive heart disease and 3 with idiopathic hypertrophic cardiomyopathy.

All subjects were examined at the two sites, Uppsala and Aarhus, with ^{11}C-acetate PET and echocardiography. Subjects were also examined with ^{11}C-PIB PET as part of a previous study (55) and the study in paper II. Subjects from Uppsala also went through ^{15}O-water PET, which is not included in the current paper.

^{11}C-acetate PET was performed according to the same protocol at the two sites. After ^{11}C-acetate injection, images were collected during 27 minutes.

Previously described methods were used to calculate myocardial oxygen consumption (MVO_2) (159). Myocardial external efficiency (MEE) was calculated through the following formula as previously described (160):

$$MEE = \frac{EW \times 1.33 \times 10^{-4}}{LV\ mass \times MVO_2 \times 20} \times 100$$

EW (external work) was calculated as the product of forward stroke volume (FSV), heart rate and mean arterial blood pressure.

Survival of CA patients was obtained and clinical, echocardiographic and ^{11}C-acetate PET parameters were examined in univariable and multivariable cox regression analysis. ROC curves were used to determine cut-off values for the ^{11}C-acetate PET parameters that best discriminated deceased from surviving CA patients. Survival analysis was performed using the established cut-off values for the ^{11}C-acetate PET parameters in all CA patients and in AL and ATTR respectively.

Paper IV

Through the pathology departments at Uppsala University Hospital and Karolinska University Hospital, we identified all samples that were assigned the code for amyloidosis (Snomed code M55100) during the time period 2000-2020. Patients not registered as inhabitants of the Uppsala and Stockholm County according to the Swedish population registry were excluded. The pathology reports were reviewed and cases with a new diagnosis of systemic AL amyloidosis during the time period were selected. If the diagnosis was uncertain from the pathology report, a review of the patient records was performed to ensure the correct diagnosis. Localized AL amyloidosis (including nodular amyloidosis of the lungs) were not included and neither were a few patients in which AL amyloidosis had been detected but who did not have any organ involvement.

Amyloid was detected through positive Congo red staining and typing was performed with immunohistochemistry or western blot. Cases with an uncertain amyloid typing were included as AL amyloidosis if they had a diagnosis of myeloma or a monoclonal protein present.

For residents in Uppsala County, all amyloid diagnostics is performed either at the specialized amyloid laboratory in Uppsala or sent to Karolinska University Hospital (renal or cardiac biopsies), and are thereby included in this study. In the Stockholm County on the other hand, smaller pathology departments might have performed amyloid diagnostics in some cases, and these may be missed in this report. That is why the cases from Uppsala County were used for incidence and prevalence calculations, and patients from Stockholm County were included in the treatment and survival analyses.

For all identified cases of systemic AL amyloidosis from Uppsala and Stockholm County a review of the patient records was performed, clinical and treatment characteristics were retrieved as well as survival time.

The incidence rate was calculated as the number of patients diagnosed each year by the population count for Uppsala County for the corresponding year. Age- and sex-adjusted incidence rate was calculated through direct standardization to the 2010 Swedish population. The 5-year limited duration prevalence was calculated for each year from 2004-2020 as the number of patients diagnosed during 5 years back in time and still alive at the end of the year of interest, divided by the population count for that year. 20-year prevalence was calculated for year 2020 using the same method. Poisson regression was used to analyse trends in incidence rate and prevalence over time. Survival analysis was performed using the Kaplan-Meier estimate and univariable and multivariable cox regression analyses were performed to examine factors influencing survival.

Ethical considerations

The studies included in this thesis were all approved by the Swedish Ethical Review Authority. The PET-studies that included patients from Aarhus, Denmark, were also approved by the Central Denmark Region Committees on Health Research Ethics. The studies followed the principles of the Declaration of Helsinki. Subjects in the PET studies (paper II and III) were given oral and written information, and signed informed consent before entering the study. These studies were also approved by the Radiation Protection Committee.

The subjects from Uppsala (healthy volunteers, hypertrophic controls and amyloidosis patients) included in paper II and III performed three PET examinations in the same session, with the tracers ^{11}C-PIB, ^{11}C-acetate and ^{15}O-water. For patients enrolled in Aarhus, ^{11}C-PIB and ^{11}C-acetate PET were performed. Together with the PET examinations, a low-dose CT scan of the chest was performed without the use of contrast agent. All three PET-tracers used were approved substances used in clinical practice (^{11}C-PIB is used in Alzheimer's disease), and except from the radiation exposure there are no known side-effects.

The radiation dose from one ^{11}C-PIB PET examination including low dose CT scan is 2.6 mSv, from ^{11}C-acetate 2.2 mSv and from ^{15}O-water 0.9 mSv. The total radiation dose was 5.7 mSv for Uppsala subjects and 4.8 mSv for Aarhus subjects, which can be put in relation to the 1-2 mSv yearly background radiation in Sweden. There were no fertile women examined in the study, and we therefore did not perform any pregnancy tests before examinations.

The subjects needed to be fasting for 4 hours before examination. Two peripheral venous catheters were inserted for tracer injection. The total time for all three PET exams was about four hours inclusive of preparations. 5 of the CA subjects also had an arterial catheter inserted for metabolite analysis, which could have caused some discomfort for the patients, and a risk of bleeding that was reduced by the procedure being performed by an experienced professional and the insertion site carefully observed.

Echocardiography was also performed in association with the PET exams, also in the healthy volunteers, this exam caused no discomfort to the subjects. If any abnormalities were found in the healthy volunteers, they were referred for further evaluation as in clinical routine.

Paper I and IV were retrospective analyses, and a substantial proportion of patients were deceased at the time of data collection. Informed consent was therefore not obtained, and was not required according to the Ethical Review Authority. The review of patient records was approved by the responsible clinic managers at the local hospitals.

Data obtained from the studies was stored in protected files, locked in at the hospital departments. Results used for presentation or publication was deidentified. For the CA and hypertrophic patients included in the PET studies, results of examinations were made available in the patient´s medical records.

In a broader perspective, PET is a relatively expensive imaging method not readily available, and if shown to be valuable in the clinic, the varying accessibility could be an ethical consideration.

Results and discussion

Paper I

During the studied time period 72 patients (39 men and 33 women) with a median age of 59 years (range 41-69) at HDM/ASCT were treated. Organ involvement was renal in 79%, cardiac in 40% and hepatic in 24%. The number of these organs involved were 1 in 57%, 2 in 31% and 3 in 8%, 4% had only gastrointestinal involvement. The patients with renal involvement had a median 24 h urine albumin of 5125 mg (range 505-27300 mg), and in patients with cardiac involvement median cardiac wall thickness was 16.5 mm (range 13-20 mm).

36% received induction therapy before HDM/ASCT, the most common regimens being vincristine/doxorubicin/dexamethasone and cyclophosphamide/dexamethasone. Bortezomib containing induction was not used in any of the patients. Median time from diagnosis to HDM/ASCT was 5.5 months in patients who received induction therapy and 3 months in patients who received HDM/ASCT directly. 97% of patients were treated with HDM/ASCT as part of first-line therapy, and the remaining two patients received HDM/ASCT due to insufficient response to primary treatment. 57% of patients received full dose (200 mg/m^2) melphalan and in the remaining patients, varying degree of dose reductions were made.

Overall response rate, at least partial organ or hematologic response, at any time point, was 64% out of all patients treated, 57% achieved organ response and 7% only hematologic response. Time to response was in median 4 months from HDM/ASCT. In responding patients, 61% had progression during the study period at a median of 3.5 years after HDM/ASCT.

Overall survival from the time of ASCT was in median 98 months (95% CI 61-135) or 8.2 years, with 5-year survival 63.9% and 10-year survival 43.4%. Median survival was significantly longer in patients without cardiac involvement, 135 months (11.3 years) versus 49 months with cardiac involvement, $p = 0.001$. Significantly longer survival was also seen in patients with one organ involved (median 135 months) compared to two or more organs (median 56 months), $p = 0.009$. There was no significant difference in survival between the patients who received induction treatment and those who did not, and neither between patients who received a higher dose of melphalan (160-200 mg/m^2) and those who received a lower dose (100-140 mg/m^2).

TRM defined as all mortality within 100 days from ASCT was 12.5%. In patients with cardiac involvement TRM was 17.2%, compared to 9.3% in patients without cardiac involvement. When comparing the earlier time period (1994-2001) to the later (2002-2009), early mortality decreased from 23.8% to 7.8%.

The study showed that long overall survival was achieved with HDM/ASCT. The median overall survival of 8.2 years is similar to the 7-10 years that has been reported from specialized amyloidosis centres (91-93). 22% of patients were alive and without disease progression or further treatment at a median follow-up time of 8.3 years (up to 14.5 years), which shows that a proportion of patients can achieve very long-term remissions. The majority of these patients (63%) had only renal involvement. Median survival in patients with only renal involvement was 13.9 years.

As expected, cardiac involvement was associated with inferior survival. So was involvement of 2 or more organs, however, in the patients with ≥ 2 organs involved, 79% had heart involvement compared to 16% in the group with one organ involved.

Unlike what has been shown in other studies (93, 97, 98), induction therapy did not improve outcome. However, no patients received bortezomib-containing induction, which has shown the greatest benefit (99). Induction therapy can serve as a test of whether the patient is fit for HDM/ASCT, and patients might have died or progressed during induction therapy. However, we did not see an increase in early deaths among patients not receiving induction therapy.

TRM decreased to 7.8% in the later part of the time period (2002-2009). This is in line with results from large amyloidosis centres; TRM of 4.4% is reported from Boston during the period 2003-2011, 6.2% from UK in 2007-2012 and 8.6% from the Mayo Clinic in 2003-2009. All centres have reported a decreasing trend in TRM which has been attributed mainly to a stricter selection of patients for HDM/ASCT. During the period of this study, cardiac biomarkers were not widely used to assess the degree of cardiac involvement but according to the grade of hypertrophy, patients with advanced cardiac involvement were probably treated.

Limitations of the study include the retrospective design which confers inconsistencies in how patients are followed, and a selection bias that leads to patients with less advanced disease being chosen for HDM/ASCT. An “intention-to-treat” analysis was not possible because only patients who went through treatment with HDM/ASCT were identified. Furthermore, the study was performed during a time-period when analysis of FLC and cardiac biomarkers were not widely used, which confers that information on the Mayo stage of patients and the rate of complete remissions are lacking. Furthermore, without the use of cardiac biomarkers, the methods for evaluating cardiac response are insensitive, probably leading to an underestimation of cardiac responses.

In conclusion, long overall survival was reached with HDM/ASCT, even in a decentralized setting. TRM was comparable to that reported from larger centres from this time period and was decreasing over time.

Paper II

At visual inspection, all of the CA patients, both AL and ATTR, were assessed as positive at ^{11}C-PIB PET, and none of the hypertrophic or healthy controls. A higher myocardium/blood SUVR was seen in CA patients compared to controls from 3.5 minutes after ^{11}C-PIB injection. At 10-20 minutes after ^{11}C-PIB injection the largest difference was seen between CA and controls, with median SUVR for AL 2.61 (IQR 2.61), ATTR 1.64 (IQR 0.62), hypertrophic controls 0.88 (IQR 0.26) and healthy controls 0.87 (IQR 0.26), $p < 0.001$ comparing CA patients to controls. RI was also significantly higher in CA than in controls ($p < 0.001$) with median RI at 10-20 minutes for AL 0.086 min^{-1} (IQR 0.075), ATTR 0.045 min^{-1} (IQR 0.014), hypertrophic controls 0.029 min^{-1} (IQR 0.005) and healthy controls 0.033 min^{-1} (IQR 0.005). There was no significant difference between the hypertrophic and healthy controls regarding SUVR ($p = 0.694$) or RI ($p = 0.054$).

ROC curves were used to determine the cut-off values of SUVR and RI that best discriminated CA from controls. The SUVR cut-off 1.09 best separated CA from controls, with AUC (area under the curve) of the ROC curve 0.98 (95% CI 0.94-1.00), sensitivity 94% (95% CI 80-99%) and specificity 93% (95% CI 66-100%). The highest sensitivity and specificity for the method was seen in AL patients where the SUVR cut-off 1.4 separated AL from controls with 100% (95% CI 88-100%) accuracy. With the RI cut-off value 0.037 min^{-1} CA could be separated from controls with a sensitivity of 94% (95% CI 80-99%) and specificity 100% (95% CI 75-100%). The RI cut-off 0.040 could completely discriminate AL from controls.

In the group of patients with systemic amyloidosis but without evidence of cardiac involvement according to echocardiography, 5 out of 11 were PET positive according to both readers, and another 3 according to one of the readers. RI was significantly higher in the predisposed group compared to controls, SUVR was numerically higher but did not reach statistical significance. In 2 of the patients (1 AL and 1 ATTR) endomyocardial biopsies were performed at follow-up, and both were positive for amyloid.

There were some correlations between clinical/echocardiography parameters and SUVR/RI shown in detail in the article.

The study confirmed that ^{11}C-PIB PET can detect cardiac amyloidosis of both AL and ATTR subtype with high accuracy. The method can distinguish cardiac amyloidosis from non-amyloid hypertrophic hearts, as well as healthy,

with high sensitivity and specificity, and may therefore be a valuable tool in the diagnosis of cardiac amyloidosis.

In the group of amyloidosis patients without increased wall thickness, there was a high prevalence of ^{11}C-PIB positivity, indicating that the method is more sensitive than echocardiography. The same finding is reported from a previous study with ^{11}C-PIB PET in ATTR mutation carriers (161).

In comparison to LGE measurement from CMR, that in a meta-analysis showed a sensitivity of 85% and specificity of 92% (162), the accuracy of ^{11}C-PIB PET seem to be at least comparable. ^{11}C-PIB binds directly to amyloid, as opposed to LGE measurement and echocardiography that mainly show indirect signs of amyloidosis, which might make this method more accurate.

Bone scintigraphy has shown high sensitivity and specificity for ATTR CA, but is often negative in AL. In contrast to bone scintigraphy, ^{11}C-PIB PET shows a higher uptake in AL patients compared to ATTR and may therefore be more useful in the diagnosis of AL CA.

There seems to be some correlations between ^{11}C-PIB uptake and clinical/echocardiographic parameters of cardiac involvement, which could indicate that the level of ^{11}C-PIB uptake is partly related to the degree of cardiac involvement. However, ^{11}C-PIB uptake also varies between amyloid fibril types. Pilebro et al showed that ^{11}C-PIB binds with varying affinity for different types (full-length and fragmented) of ATTR fibrils (161). The level of ^{11}C-PIB uptake in AL cases are even more varying than in ATTR, which could indicate differences in ^{11}C-PIB binding depending on the individual fibril structure in AL patients as well.

The degree of ^{11}C-PIB uptake could also be influenced by myocardial blood flow, which could cause less ^{11}C-PIB to be delivered to the tissue. This could contribute to the lower ^{11}C-PIB uptake seen in ATTR since these patients have thicker cardiac walls and thereby possibly lower perfusion. However, a previous pilot-study could not show any association between ^{11}C-PIB uptake and myocardial perfusion measured with ^{11}C-acetate PET (55).

In this study, visual inspection was more accurate than the semi-quantitative measures SUVR and RI. This can be due to heterogenous amyloid deposition that might be missed in SUVR and RI measurement. It may also be easier visually to distinguish uptake in myocardium from spill-in from surrounding tissues. If visual assessment is inconclusive, we recommend the use of the simple measure SUVR at 10-20 minutes after ^{11}C-PIB injection at first hand, and using the stated cut-off value 1.09.

Limitations of the study include the relatively small number of subjects when divided into amyloid subtypes, especially in the prospective group, and also the varying disease stages of patients with the majority of AL patients having received treatment that could possibly affect ^{11}C-PIB uptake.

In conclusion, ^{11}C-PIB PET was highly accurate in detecting CA, especially AL, and could be a useful method to rule in or out amyloidosis in patients with unexplained diastolic heart failure. Findings also indicated

that ^{11}C-PIB PET can detect CA at an earlier stage compared to echocardiography and might be a useful tool for early diagnosis of CA.

Paper III

MVO_2 was significantly reduced in CA patients compared to healthy controls (0.08 vs 0.10 mL/min/g, p = 0.003), but not significantly different in CA compared to hypertrophic controls. MVO_2 did not differ significantly between AL and ATTR (0.08 vs 0.07 mL/min/g, p = 0.252), and was not significantly different in surviving compared to deceased CA patients, neither in AL nor in ATTR.

MEE was significantly lowered in CA compared to both hypertrophic and healthy controls (14 vs 28 and 27% respectively, p <0.001), but without significant difference between deceased and surviving CA patients. There was no significant difference between AL and ATTR patients.

The ratio of FSV and LVM from ^{11}C-acetate PET was also significantly reduced in CA, compared to both hypertrophic and healthy controls (0.29 vs 0.58 and 0.82 mL/g, p = <0.001) and also significantly lowered in deceased patients compared to survivors. FSV/LVM was significantly lower in ATTR compared to AL.

In ROC analysis the best cut-off value of MEE in discriminating deceased from surviving CA patients was 15.7% with AUC 0.63 (95% CI 0.47-0.79). FSV/LVM was the ^{11}C-acetate PET parameter that best discriminated deceased from surviving, both AL and ATTR patients. The optimal prognostic cut-off value was 0.27 mL/g with AUC 0.72 (95% CI 0.57-0.87), in AL patients the best cut-off was 0.39 mL/g.

When using the cut-off values above, survival was significantly longer with high MEE and FSV/LVM compared to low (p = 0.032 and p < 0.001 respectively). When analysing AL and ATTR separately there was a significant survival difference with high compared to low FSV/LVM, but not significant for MEE.

In univariable analysis, NYHA-class, Nt-proBNP and the ^{11}C-acetate PET parameters FSV/LVM and MEE were the strongest prognostic factors. Out of the ^{11}C-acetate PET parameters, FSV/LVM was the strongest survival predictor with hazard ratio 0.56 per 0.1 mL/g (95% CI 0.39-0.81, p = 0.002), and independently prognostic in a multivariable model including the strongest prognostic ^{11}C-acetate PET parameters MEE and FSVI. FSV/LVM remained significantly prognostic in bivariable analysis with all the other univariable predictors.

The study showed that MEE and FSV/LVM are reduced in cardiac amyloidosis and that lower levels of both MEE and FSV/LVM are associated with inferior survival. The ^{11}C-acetate PET parameter that best predicted survival was

FSV/LVM, this measure is similar to MCF that was previously shown to be prognostic in CA (139). MCF is calculated as LV stroke volume by LV myocardial volume, and usually the geometric total SV is used, and not the forward SV. This might be a disadvantage with MCF, since the presence of valvular insufficiencies often seen in CA is not taken into account.

With increasing amyloid burden, the stroke volume decreases and mass increases, which should make FSV/LVM a sensitive marker of disease progression. FSV/LVM was lowered in the surviving CA patients as well, which suggests that it is not only a marker of advanced disease. In a previous study, SV had a high probability of being abnormal from early disease stages and MCF had a progressively increasing likelihood of being abnormal with higher amyloid burden (139).

In this study, FSV/LVM was a better prognostic marker than all the echocardiographic parameters. However, due to the retrospective nature of the study, LS was missing in a substantial proportion of CA patients (11 out of 48), and was therefore not included in the survival analyses. LS has previously been shown to be highly prognostic in CA (134).

MEE was significantly reduced in CA, which reflects poor energetic efficiency. The measure incorporates FSV/LVM and also MVO_2. The inclusion of oxidative metabolism did not seem to add prognostic value to MEE in either subtype of CA. However, MVO_2 is measured in relation to myocardial mass, which in amyloidosis consists not only by viable myocytes but also extracellular amyloid deposition that is not contributing to the oxygen metabolism. If correction for extracellular mass was performed, MVO_2 would probably be higher.

FSV/LVM or MCF can be measured with other PET perfusion tracers, as well as with CMR or echocardiography, and in patients that are evaluated for cardiac symptoms lowered values might be indicative of cardiac amyloidosis.

Limitations of the study include the low patient numbers, especially when separated in AL and ATTR, the groups are too small to draw conclusions about differences between the subtypes. Different mechanisms are involved in AL compared to ATTR CA, including more blood vessel involvement as well as toxic effects on the myocytes in AL amyloidosis, making it reasonable to analyse the two groups separately. Furthermore, including measurement of ECV by for example using combined PET/CMR would be valuable for correction of MVO_2 for different levels of ECV.

In conclusion, reduced MEE was associated with shorter survival in CA patients, but FSV/LVM was the strongest survival predictor and the only independently prognostic ^{11}C-acetate PET parameter in multivariable analysis.

Paper IV

During 2000-2020 a total of 302 new cases of systemic AL amyloidosis were identified, 76 from Uppsala and 226 from Stockholm County. The crude incidence rate for Uppsala County was 10.8 (95% CI 8.6-13.5) per million person-years, and the age- and sex-adjusted incidence rate was 12.0 per million person-years (95% CI 9.3-14.7). There was no significant change in the incidence rate during the studied time period, $p = 0.153$. The 5-year limited duration prevalence increased numerically during the period from 9.9 cases per million inhabitants in 2004 to 38.6 in 2020, but the trend was not statistically significant ($p = 0.434$). The 20-year prevalence for 2020 was 48.9 (95% CI 31.3-76.4) per million inhabitants for Uppsala County.

Baseline and treatment characteristics are presented in detail in the manuscript. Comparing the earlier part of the studied time period (2000-mid 2010) to the later (mid 2010-2020), significantly fewer patients were diagnosed at autopsy in the later period, and the proportion of patients receiving palliative treatment was significantly lower. First-line therapy differed markedly between the time periods, with a significant increase in the use of proteasome inhibitor, IMiD and CD38-anibody based treatments in the later time period, and a decrease in the use of chemotherapy based regimens (except for high dose chemotherapy). The use of high dose therapy was not significantly different between time periods, but induction therapy before HDM/ASCT was used more in the later period.

Median overall survival from the time of diagnosis was 21 months (95% CI 14.5-27.5). In the later time period survival was significantly longer than in the early period, 28 months (95% CI 18.3-37.7) compared to 13 months (95% CI 7.6-18.4), $p < 0.001$. Significantly shorter survival was seen in patients with cardiac involvement (HR 2.04, 95% CI 1.41-2.93, $p < 0.001$) and in patients aged > 70 years at diagnosis (HR 1.54, 95% CI 1.16-2.06, $p = 0.003$). Patients who underwent high dose chemotherapy had superior survival (HR 0.30, 95% CI 0.17-0.53, $p < 0.001$), median survival in patients receiving high dose therapy was 266 months (95% CI 77.5-454.5) or 22.2 years.

Mortality within 6 months from diagnosis was less frequent in the later time period compared to the earlier (25.6% vs 38.2%, $p = 0.022$). Heart involvement and not receiving high dose therapy was associated with increased risk of early death, and causes of early death were predominantly heart related. TRM defined as all death within 100 days of ASCT was reduced from 15.8% in the early time period to 5.3% in the late period.

In this study that included only confirmed cases of systemic AL amyloidosis, we showed that the standardized incidence was 12.0 (95% CI 9.3-14.7) per million person-years for Uppsala County of Sweden, which is consistent with the incidence of 12 (95% CI 8-16) per million person-years previously

reported from Olmsted County, Minnesota using similar methodology (26). The incidence did not change significantly during the studied time period.

We believe that this study as near as possible captures all cases diagnosed with AL amyloidosis in this region, and since only confirmed cases are included, accuracy should be higher than for incidence reports based on estimations from registries. Since the incidence is consistent with that reported from Olmsted County, Minnesota it should be generalizable to populations of the Western world. However, there are indications of varying incidence of plasma-cell disorders including AL amyloidosis between ethnicities, and the incidence could probably not be applicable to all populations globally.

With regards to the prolonged survival that is reported in our and other studies, an increase in prevalence would be expected over time. In our study we could not show any statistically significant increase in the 5-year prevalence during the studied time period. Other studies have reported an increasing prevalence of AL amyloidosis over time (28, 30, 34).

This study includes a truly population-based cohort of patients, which is reflected by the higher median age, larger proportion of patients receiving palliative treatment, and inferior survival compared to what is reported from a European observational study (2). In our study there was a significant reduction in patients diagnosed at autopsy, and in patients receiving palliative treatment between the early and late part of the time period, which can indicate that patients are being diagnosed at an earlier disease stage. There has also been a shift in treatment pattern between the early and late time period, that has probably contributed to the significant improvement in survival that is observed.

There was also a significant reduction in early mortality (< 6 months from diagnosis) in the later time period, which is encouraging since the European study mentioned above reported consistently high early mortality over time (2). The reduction in early deaths is probably mainly due to earlier diagnosis. In the randomized ANDROMEDA study, more effective treatment with the addition of daratumumab did not affect early mortality (< 60 days from starting treatment), so the change in treatment patterns has probably impacted less on the reduced early mortality. As expected, cardiac involvement was the most important risk factor for both overall and early mortality.

Treatment with HDM/ASCT was associated with better prognosis, both long-term and within 6 months from diagnosis. This is likely at least partly due to selection of patients with less advanced organ involvement for HDM/ASCT. There was a significant reduction in TRM between the early and late time period, which can indicate more adequate patient selection. The frequency of HDM/ASCT did not differ significantly between time periods, but if patients generally were diagnosed earlier, there could have been a selection of patients with less advanced disease for HDM/ASCT. The use of induction therapy, and mainly bortezomib based induction was also higher in the later

time period, which has previously been associated with improved outcome after HDM/ASCT (93).

Limitations of the study include the homogenous population with the vast majority being of Caucasian origin, reducing the generalizability of the incidence to other populations. Although this study was based on around twice as many cases as the previous comparable incidence study from Olmstead County (26), the number is still quite small. We also lack information on important prognostic factors such as cardiac stage and treatment response.

In conclusion, we could determine the standardized incidence for systemic AL amyloidosis to 12.0 (95% CI 9.3-14.7) per million person years for Uppsala County, which is consistent with previous similar reports. There was no significant change in the incidence rate over time. A numerical increase in the 5-year prevalence was observed, but the trend was not statistically significant. Prolonged overall survival and decreased early mortality was seen over time.

Concluding remarks and further perspectives

In **paper I** we could confirm that long overall survival and long-term remissions can be obtained with HDM/ASCT in AL amyloidosis, also in decentralized settings. The rate of TRM is decreasing over time and, as shown in paper IV and other studies, has continued to decrease. TRM is getting close to what is seen with HDM/ASCT in myeloma, indicating that the current selection criteria are accurate. In paper IV, that included a later time period, we could also show that median survival in high dose treated patients was as long as 22 years.

However, with the recently introduced more effective first-line therapy daratumumab-VCd, 53% of patients reached CR. The current recommendation is not to proceed to HDM/ASCT if CR is already reached, even though there is lack of data on PFS with daratumumab-VCd only, compared to HDM/ASCT. With regards to the effectiveness of the current standard first-line treatment, results regarding PFS from a randomized study would take time, and validated surrogate endpoints are currently lacking. MRD with bone marrow flow cytometry is used in myeloma, but studies indicate that this is not a highly sensitive measure of deep response in AL amyloidosis, and more studies are needed on blood mass spectrometry in this situation. According to paper IV the frequency of high dose treatment was not significantly different between time periods. However, the most recent time period, after introduction of the daratumumab-VCd treatment and updated treatment guidelines, was not included and likely the rate of high dose therapy will decrease.

In **paper IV** we could show that the population-based incidence of AL amyloidosis in Sweden is around 12 per million person-years and has not changed significantly over the last two decades. Our study indicates that there is still an underdiagnosis since a proportion of patients are not diagnosed until autopsy, and that patients are still diagnosed in late stages of cardiac involvement when prognosis is poor. This again highlights the need for increased awareness of this disease, especially among cardiologists. The increasing treatment possibilities in both AL and ATTR will hopefully lead to more patients being evaluated for cardiac amyloidosis in general. When investigating patients with possible CA, looking for a monoclonal protein should be done early as a screening method for AL, as well as bone scintigraphy for ATTR. In unclear cases, our study (**paper II**) shows that ^{11}C PIB PET can be used to rule in or out CA, especially of AL subtype, with high accuracy. Our and other studies

have shown that amyloid PET as well as CMR can detect cardiac AL amyloidosis earlier than echocardiography, and even earlier than Nt-proBNP according to a study by Cohen et al (63). Recently, consensus guidelines (47) have included typical findings on amyloid PET or CMR as criteria for cardiac involvement of AL amyloidosis.

However, the exact role for PET and CMR in CA diagnostics is not yet established, and studies are lacking directly comparing the accuracy of the two methods. Availability and cost may also be issues with both of these modalities compared to echocardiography. Regarding CMR, ECV measurement has shown higher accuracy compared to LGE in detecting CA, with a sensitivity of 89% and specificity of 98.6% reported from a meta-analysis including both AL and ATTR CA (163). Furthermore, T1 and T2 mapping has shown high diagnostic performance (164), with the advantage of not requiring contrast. Amyloid PET might have the advantage of possibly being able to distinguish between amyloid subtypes. A study with ^{18}F-florbetaben showed delayed tracer uptake in AL patients compared to ATTR, that could differentiate the two groups (56). A potential role of ECV measurement in follow-up after treatment has been shown (157, 158), whereas the possible role of amyloid PET in follow-up after treatment has not yet been evaluated.

When it comes to prognostication of cardiac AL amyloidosis, we could show in **paper III** that the ^{11}C-acetate PET parameter FSV/LVM is highly prognostic in CA. This measure can be obtained from other imaging modalities as well, and except from being a prognostic marker it might serve as an indication of possible CA diagnosis. Both PET and CMR can be used to non-invasively assess the coronary flow reserve, in the investigation of patients with suspected coronary syndromes (165). In this situation, the finding of a lowered FSV/LVM can give an indication of cardiac amyloidosis.

In our study we were not able to compare FSV/LVM to the other proposed prognostic imaging parameters LS and ECV, and we did not have enough AL patients to draw robust conclusions in this group separately. The pathophysiology of cardiac amyloidosis is complex, especially in the AL subtype, several mechanisms leading to cardiac dysfunction are involved. Compared to ATTR, AL patients have more vascular amyloid deposition, higher grade of myocardial oedema and more toxic effects on the myocytes involved. The degree of influence of these various components may vary between AL patients, and also at different stages of the disease. To evaluate the effects on for example oxidative metabolism, larger study groups are needed, and also combined PET/CMR studies to be able to correct for ECV.

Populärvetenskaplig sammanfattning på svenska

Amyloidos är en grupp sjukdomar som kännetecknas av inlagring av amyloid (aggregat av olika typer av proteiner) i olika organ i kroppen. Detta leder till att organen med tiden fungerar allt sämre. Vilken slags amyloidos det rör sig om definieras utifrån den typ av protein som lagrats in. Den allmänt mest kända amyloidossjukdomen är Alzheimers sjukdom där proteinet beta-amyloid lagras in i hjärnan. När det gäller systemisk amyloidos som drabbar flera organ i kroppen är lättkedje (AL) och transthyretin (ATTR) amyloidos de två vanligaste typerna.

Vid AL-amyloidos är den grundläggande orsaken en patologisk klon av plasmaceller (antikroppsbildande vita blodkroppar) i benmärgen som producerar avvikande lätta immunglobulinkedjor, det vill säga delar av antikroppar. Dessa har förmågan att bilda amyloidstruktur och lagras in i olika organ. Orsaken till att man drabbas av sjukdomen är okänd. Det är en ovanlig sjukdom som är något vanligare hos män än hos kvinnor, och oftast drabbar personer i 60–70 års åldern.

Hjärtat är ett av de vanligaste organen som kan drabbas vid både AL- och TTR-amyloidos vilket är särskilt allvarligt på grund av hög dödlighet i hjärtsvikt och rytmrubbningar. Vid AL-amyloidos ses hjärtengagemeng hos cirka 80% och graden av hjärtpåverkan är den viktigaste faktorn för överlevnad vid sjukdomen. Sjukdomen kan indelas i stadier utifrån framför allt nivån av hjärtbiomarkörer, vilket ger information om prognosen. Vid det svåraste stadiet som betecknas IIIb är överlevnaden endast cirka 6 månader trots behandling.

AL-amyloidos kan yttra sig på en mängd olika sätt beroende på vilka organ som drabbas, och fynden vid undersökningar är inte specifika för sjukdomen. Därför är det vanligt att diagnosen fördröjs och att patienterna har utvecklat en allvarlig organpåverkan när diagnosen ställs. Detta medför sämre möjlighet för patienten att tolerera behandling, och mindre chans att organfunktionen ska kunna återhämta sig. Det är alltså viktigt att diagnosen ställs tidigt i förloppet för prognosen vid sjukdomen.

Dagens behandling riktar sig mot de avvikande plasmacellerna i benmärgen, som är grundorsaken till sjukdomen. Cellgifter av olika typ används liksom modernare mer riktade typer av behandlingar.

Arbete I syftade till att undersöka långtidsresultaten av högdos cellgiftsbehandling (melfalan), med stöd av egna stamceller, vid AL-amyloidos.

Behandlingen är omdiskuterad på grund av den höga dödligheten i samband med behandling som tidigare har rapporterats. Studier från specialiserade amyloidoscentra har visat minskad dödlighet vid behandling på senare tid, och bättre resultat om behandling utförs vid centra med hög erfarenhet. Någon tidigare studie av behandlingsresultat från Sverige, där denna vård är decentraliserad, har inte gjorts. Studien syftade till att utvärdera effekt, överlevnad och behandlingsrelaterad mortalitet efter högdos cellgiftsbehandling vid AL-amyloidos, och om någon förändring avseende dödlighet i samband med behandling har skett över tid i Sverige.

Vi fann att 64% av patienterna hade effekt av behandlingen. Överlevnaden från behandling var i median 8,2 år, med 5-årsöverlevnad 63,9% och 10-årsöverlevnad 43,4%. Längre överlevnad sågs hos de patienter som inte hade hjärtengagemang, och hos de där endast ett organ var påverkat av amyloidos. Vi fann ingen säker skillnad beroende av om förbehandling med cellgifter gavs innan högdosbehandlingen eller inte, och inte heller beroende av om full dos melfalan eller reducerad dos gavs. Dödligheten inom 100 dagar från stamcellsinfusion var 12,5%, och högre hos patienter med hjärtengagemang. Sett över tid minskade dödligheten från 23,8% under den tidigare delen av den studerade perioden jämfört med 7,8% under den senare.

I **arbete II** undersökte vi en ny metod för att diagnostisera hjärtamyloidos i ett tidigt skede. Avbildningsmetoden positronemissionstomografi (PET) med spårämnet ^{11}C-PIB har använts för att påvisa amyloidos vid Alzheimers sjukdom. ^{11}C-PIB binder till amyloid av olika typer, och har i pilotstudier visats kunna påvisa amyloidos i hjärtat. I studien undersökte vi 36 patienter med hjärtamyloidos, både AL och ATTR, samt 8 friska kontroller och 7 kontroller med förtjockat hjärta av annan orsak än amyloidos. Samtliga forskningspersoner genomgick PET av hjärtat med användning av spårämnet ^{11}C-PIB, samt även hjärtultraljud. Upptaget av ^{11}C-PIB i hjärtat värderades både visuellt som positivt/negativt och genom beräkning av måtten SUVR och RI vilka ger en kvantifiering av ^{11}C-PIB-upptaget. De gränsvärden för SUVR och RI som bäst skiljde ut patienterna med hjärtamyloidos från kontrollerna applicerades sedan på en grupp amyloidospatienter utan diagnostiserat hjärtengagemang enligt gängse kriterier. Alla undersökningar utvärderades blindat av två oberoende observatörer med expertis inom hjärt-PET.

Vi fann att alla patienter med hjärtamyloidos var positiva vid PIB-PET utifrån den visuella bedömningen, men ingen av kontrollerna, varken de friska eller de med hjärtförtjockning av annan orsak. Både SUVR och RI var högre hos hjärtamyloidos patienterna jämfört med kontrollerna. SUVR-gränsvärdet 1,09 kunde skilja hjärtamyloidos från kontroller med högst sensitivitet (94%) och specificitet (93%), och för RI gav tröskelvärdet 0,037 min^{-1} högst sensitivitet (94%) och specificitet (100%). Högre sensitivitet och specificitet för båda måtten sågs hos AL patienter jämfört med ATTR. I gruppen utan diagnostiserat hjärtengagemang var 5 av 11 positiva vid visuell bedömning av

båda observatörerna. Hos två av de PET-positiva patienterna utfördes hjärtbiopsi vid uppföljning som utföll positivt för amyloidos.

Arbete III syftade till att utvärdera om mått på hjärtats verkningsgrad (MEE, myocardial external efficiency) kan användas för prognostisk information vid hjärtamyloidos. PET av hjärtat med spårämnet ^{11}C-acetat kan användas för att mäta hjärtats syrgasförbrukning och ger även mått på mekaniskt arbete såsom slagvolym. Därmed kan hjärtats verkningsgrad beräknas. Kvoten mellan slagvolym och vänsterkammarmassa har i tidigare studier visats vara prognostiskt vid hjärtamyloidos. Vi ville undersöka om hjärtats syrgasförbrukning och verkningsgrad bättre kunde förutsäga överlevnad. 48 patienter med hjärtamyloidos (både AL och ATTR), samt 20 kontroller undersöktes med ^{11}C-acetat PET och hjärtultraljud. Patienterna följdes upp med avseende på överlevnad. Parametrar från undersökningarna utvärderades statistiskt vad gäller deras inverkan på överlevnaden.

Studien visade att MEE var sänkt hos patienterna med hjärtamyloidos jämfört med kontrollerna, men utan statistiskt säkerställd skillnad mellan de som avlidit och de överlevande. Det tröskelvärde avseende MEE som bäst kunde skilja de avlidna från de överlevande var 15,7%. Överlevnaden var sämre för patienterna med MEE <15,7% jämfört med för de med MEE>15,7%, dock var skillnaden inte statistiskt säkerställd när AL- och ATTR-amyloidos analyserades var för sig. Bäst separation mellan avlidna och överlevande erhölls med kvoten mellan slagvolym och massa (FSV/LVM) där patienter med nivå under tröskelvärdet 0,27 ml/g hade tydligt sämre överlevnad, en skillnad som var statistiskt säkerställd även för AL- och ATTR-amyloidos för sig. När effekten på överlevnad av flera ^{11}C-acetat PET parametrar undersöktes tillsammans, fann vi att FSV/LVM var det mått som bäst kunde förutsäga överlevnaden.

I **arbete IV** ville vi undersöka förekomsten och överlevnaden av AL-amyloidos i Sverige, detta då det råder brist på sådana populationsbaserade epidemiologiska studier inom AL-amyloidos. Eftersom sjukdomen alltid diagnostiseras med vävnadsbiopsi sökte vi efter alla patienter som under perioden år 2000–2020 erhållit diagnosen amyloidos i databaserna på patologlaboratorierna vid Akademiska sjukhuset i Uppsala och Karolinska sjukhuset i Stockholm. Alla utlåtanden från vävnadsbiopsierna granskades, och för alla oklara fall utifrån patologutlåtandet liksom alla identifierade fall av AL-amyloidos utfördes journalgranskning. Endast patienter folkbokförda i Uppsala respektive Stockholms län med verifierad nydiagnostiserad AL-amyloidos under den aktuella tidsperioden inkluderades. Incidensen (antal nya fall per invånare och år) och prevalensen (antal som lever med diagnosen efter en viss tidsperiod) samt överlevnaden undersöktes, liksom eventuell förändring över tid.

Vi fann en incidens av systemisk AL-amyloidos, standardiserad utifrån befolkningens ålder och kön, på 12 nya fall per miljon invånare och år. Incidensen ökade inte signifikant under perioden. 5-års prevalensen ökade under perioden, men trenden var inte statistiskt säkerställd. Medianöverlevnaden från diagnos var 21 månader, och ökade från 13 månader för patienter

diagnostiserade under den tidigare delen av tidsperioden till 28 månader under den senare delen. Sämre överlevnad sågs hos patienter med hjärtengagemang, ålder> 70 år vid diagnos och hos patienter som inte genomgick högdos cellgiftsbehandling. Tidig dödlighet inom 6 månader från diagnos minskade från 38,2% under den tidigare delen av tidsperioden, till 25,6% under den senare delen.

Sammanfattningsvis har denna avhandling bidragit med kunskap inom epidemiologi, diagnostik, behandling och prognostisering vid AL-amyloidos, särskilt när det gäller patienter med hjärtengagemang. Vi har visat att goda resultat kan uppnås med högdos cellgiftsbehandling vid AL-amyloidos även vid decentraliserad vård. Dock är det i dagsläget oklart hur denna behandling står sig i relation till modern konventionell behandling, där jämförande studier hittills saknas. Vi har även visat att PET med spårsubstansen ^{11}C-PIB är en metod som kan diagnostisera hjärtamyloidos med mycket hög träffsäkerhet. Metodens plats i relation till andra diagnostiska metoder vid hjärtamyloidos behöver dock studeras ytterligare. När det gäller faktorer som kan förutsäga överlevnad vid hjärtamyloidos visar vår och andras studier att kvoten mellan slagvolym och vänsterkammarmassa är starkt prognostisk för överlevnad, och kan addera information till kända prognostiska markörer. Vi har även kunnat beräkna incidensen av AL-amyloidos i Sverige, och visa att den totala liksom den tidiga överlevnaden har förbättrats över tid vilket indikerar att tidigare diagnostik och förbättrad behandling av patienterna har givit resultat.

Acknowledgements

My warmest thanks to:

Kristina Carlson for your patience with me and for all the knowledge, clever thoughts and common sense that you have shared. Your burning interest in medicine and in our patients is a true inspiration.

Jens Sörensen for teaching me everything that I know about cardiac PET, for having patience and trust in me, and for all the interesting talks.

All other co-workers within the field of amyloidosis: **Per Westermark**, **Ulrika Thelander**, **Justina Damjanovic Vesterlund**, **Gunnar Antoni**, **Tanja Kero**, **Tomasz Baron**, **Frank Flachskampf**, **Gerhard Wikström**, **Spyridon Gerovasileiou**, **Erik Björklund** and **Birgitta Jönelid**, as well as **Tor Skibstedt Clemmensen** with colleagues at Aarhus University Hospital for fruitful and friendly collaboration.

Patients and **volunteers** who participated in the studies.

Swedish Heart-Lung Foundation for financial support of the PET studies.

Bengt Smedmyr, **Honar Cherif** and **Gunnar Larfors**, my past and present clinic managers, for giving me the opportunity to continue this work, even though it has taken a long time.

All former and present colleagues at the Department of Haematology: **Emma Bergfeldt Lennmyr**, **Elisabeth Ejerblad**, **Helene Hallböök**, **Martin Höglund**, **Torbjörn Karlsson**, **Karin Larsson**, **Sören Lehmann**, **Mattias Mattsson**, **Daniel Moreno Berggren**, **Ulla Olsson Strömberg**, **Klara Svedevall**, **Stina Söderlund**, **Tobias Tolf**, **Sofia Vikman**, **Anna Robelius** and **Albin Österroos**. I am so impressed by all of you, and it is a pleasure working with you all.

Franco Pasquariello for inspiring me to become a haematologist.

Karolina Ekman for all the fun times within haematology and otherwise.

Cecilia Jönsson, **Ylva Norén** and **Johanna Roos** for long-lasting friendship that means so much to me.

Mom and **dad**, you have always been there for me. **Linda** and **Andrea**, I am so impressed by both of you.

Peter for everything that you do for me, from help with statistics to making sure that I eat properly. You are always there to help and there is nothing that you cannot fix. You are always by my side and I am so grateful for that.

Anja and **Bruno**. Ni är bäst!

References

1. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. Advances in Therapy. 2015;32(10):920-8.
2. Palladini G, Schönland S, Merlini G, Milani P, Jaccard A, Bridoux F, et al. The management of light chain (AL) amyloidosis in Europe: clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018. Blood Cancer Journal. 2023;13(1).
3. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood. 2017;129(15):2111-9.
4. Staron A, Zheng L, Doros G, Connors LH, Mendelson LM, Joshi T, et al. Marked progress in AL amyloidosis survival: a 40-year longitudinal natural history study. Blood Cancer Journal. 2021;11(8).
5. Riek R, Eisenberg DS. The activities of amyloids from a structural perspective. Nature. 2016;539(7628):227-35.
6. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349(6):583-96.
7. Larsen BT, Mereuta OM, Dasari S, Fayyaz AU, Theis JD, Vrana JA, et al. Correlation of histomorphological pattern of cardiac amyloid deposition with amyloid type: a histological and proteomic analysis of 108 cases. Histopathology. 2016;68(5):648-56.
8. Merlini G, Stone MJ. Dangerous small B-cell clones. Blood. 2006;108(8):2520-30.
9. Cuenca I, Alameda D, Sanchez-Vega B, Gomez-Sanchez D, Alignani D, Lasa M, et al. Immunogenetic characterization of clonal plasma cells in systemic light-chain amyloidosis. Leukemia. 2021;35(1):245-9.
10. Huang X-F, Jian S, Lu J-L, Shen K-N, Feng J, Zhang C-L, et al. Genomic profiling in amyloid light-chain amyloidosis reveals mutation profiles associated with overall survival. Amyloid. 2020;27(1):36-44.
11. Blancas-Mejia LM, Misra P, Dick CJ, Cooper SA, Redhage KR, Bergman MR, et al. Immunoglobulin light chain amyloid aggregation. Chemical Communications. 2018;54(76):10664-74.
12. Kourelis TV, Dasari S, Theis JD, Ramirez-Alvarado M, Kurtin PJ, Gertz MA, et al. Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry. Blood. 2017;129(3):299-306.
13. Poshusta TL, Sikkink LA, Leung N, Clark RJ, Dispenzieri A, Ramirez-Alvarado M. Mutations in specific structural regions of immunoglobulin light chains are associated with free light chain levels in patients with AL amyloidosis. PLoS One. 2009;4(4):e5169.

14. Radamaker L, Karimi-Farsijani S, Andreotti G, Baur J, Neumann M, Schreiner S, et al. Role of mutations and post-translational modifications in systemic AL amyloidosis studied by cryo-EM. Nature Communications. 2021;12(1).
15. Alameda D, Goicoechea I, Vicari M, Arriazu E, Nevone A, Rodriguez S, et al. Tumor cells in light-chain amyloidosis and myeloma show distinct transcriptional rewiring of normal plasma cell development. Blood. 2021;138(17):1583-9.
16. Dispenzieri A, Larson DR, Rajkumar SV, Kyle RA, Kumar SK, Kourelis T, et al. N-glycosylation of monoclonal light chains on routine MASS-FIX testing is a risk factor for MGUS progression. Leukemia. 2020;34(10):2749-53.
17. Nevone A, Girelli M, Mangiacavalli S, Paiva B, Milani P, Cascino P, et al. An N-glycosylation hotspot in immunoglobulin κ light chains is associated with AL amyloidosis. Leukemia. 2022;36(8):2076-85.
18. Blancas-Mejia LM, Ramirez-Alvarado M. Systemic amyloidoses. Annu Rev Biochem. 2013;82:745-74.
19. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood. 1992;79(7):1817-22.
20. Pinney JH, Smith CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SDJ, et al. Systemic Amyloidosis in England: an epidemiological study. British Journal of Haematology. 2013;161(4):525-32.
21. Aguirre MA, Boietti BR, Nucifora E, Sorroche PB, González Bernaldo De Quirós F, Giunta DH, et al. Incidence rate of amyloidosis in patients from a medical care program in Buenos Aires, Argentina: a prospective cohort. Amyloid. 2016;23(3):184-7.
22. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. Ann Med. 2008;40(3):232-9.
23. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015;36(38):2585-94.
24. Bennani Smires Y, Victor G, Ribes D, Berry M, Cognet T, Méjean S, et al. Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy. The International Journal of Cardiovascular Imaging. 2016;32(9):1403-13.
25. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J. 2017;38(38):2879-87.
26. Kyle RA, Larson DR, Kurtin PJ, Kumar S, Cerhan JR, Therneau TM, et al. Incidence of AL Amyloidosis in Olmsted County, Minnesota, 1990 through 2015. Mayo Clinic Proceedings. 2019;94(3):465-71.
27. Hou H-A, Tang C-H, Goh CH, Shen S-P, Huang K-C, Qiu H, et al. A population-based cohort study of the epidemiology of light-chain amyloidosis in Taiwan. Scientific Reports. 2022;12(1).
28. Mellqvist UH, Cai Q, Hester LL, Grovdal M, Borsum J, Rahman I, et al. Epidemiology and clinical outcomes of light-chain amyloidosis in Sweden: A nationwide population-based study. Eur J Haematol. 2023;111(5):697-705.

29. Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Incidence and survival in non-hereditary amyloidosis in Sweden. BMC Public Health. 2012;12(1):974.
30. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Advances. 2018;2(10):1046-53.
31. Landgren O, Graubard BI, Katzmann JA, Kyle RA, Ahmadizadeh I, Clark R, et al. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutritional Examination Survey. Leukemia. 2014;28(7):1537-42.
32. Landgren O, Gridley G, Turesson I, Caporaso NE, Goldin LR, Baris D, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. Blood. 2006;107(3):904-6.
33. Staron A, Connors LH, Zheng L, Doros G, Sanchorawala V. Race/ethnicity in systemic AL amyloidosis: perspectives on disease and outcome disparities. Blood Cancer Journal. 2020;10(11).
34. Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. Global epidemiology of amyloid light-chain amyloidosis. Orphanet Journal of Rare Diseases. 2022;17(1).
35. Muchtar E, Dispenzieri A, Lacy MQ, Buadi FK, Kapoor P, Hayman SR, et al. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. Ann Med. 2017;49(7):545-51.
36. Kourelis TV, Kumar SK, Gertz MA, Lacy MQ, Buadi FK, Hayman SR, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol. 2013;31(34):4319-24.
37. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology. 2014;15(12):e538-e48.
38. Geller HI, Singh A, Mirto TM, Padera R, Mitchell R, Laubach JP, et al. Prevalence of Monoclonal Gammopathy in Wild-Type Transthyretin Amyloidosis. Mayo Clin Proc. 2017;92(12):1800-5.
39. Benson MD, Berk JL, Dispenzieri A, Damy T, Gillmore JD, Hazenberg BP, et al. Tissue biopsy for the diagnosis of amyloidosis: experience from some centres. Amyloid. 2022;29(1):8-13.
40. Schonland SO, Hegenbart U, Bochtler T, Mangatter A, Hansberg M, Ho AD, et al. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. Blood. 2012;119(2):488-93.
41. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR, 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957-9.
42. Vrana JA, Theis JD, Dasari S, Mereuta OM, Dispenzieri A, Zeldenrust SR, et al. Clinical diagnosis and typing of systemic amyloidosis in subcutaneous fat aspirates by mass spectrometry-based proteomics. Haematologica. 2014;99(7):1239-47.
43. Arbustini E, Verga L, Concardi M, Palladini G, Obici L, Merlini G. Electron and immuno-electron microscopy of abdominal fat identifies and characterizes amyloid fibrils in suspected cardiac amyloidosis. Amyloid. 2002;9(2):108-14.

44. Damjanovic Vesterlund J, Ihse E, Thelander U, Zancanaro A, Westermark GT, Westermark P. Tissue-based diagnosis of systemic amyloidosis: Experience of the informal diagnostic center at Uppsala University Hospital. Ups J Med Sci. 2022;127.
45. Palladini G, Russo P, Bosoni T, Verga L, Sarais G, Lavatelli F, et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. Clin Chem. 2009;55(3):499-504.
46. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. 2005;79(4):319-28.
47. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 2 of 2—Diagnostic Criteria and Appropriate Utilization. Circulation: Cardiovascular Imaging. 2021;14(7).
48. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol. 2005;95(4):535-7.
49. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. Am J Cardiol. 2014;114(7):1089-93.
50. Siqueira-Filho AG, Cunha CL, Tajik AJ, Seward JB, Schattenberg TT, Giuliani ER. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. Circulation. 1981;63(1):188-96.
51. Liu D, Niemann M, Hu K, Herrmann S, Stork S, Knop S, et al. Echocardiographic evaluation of systolic and diastolic function in patients with cardiac amyloidosis. Am J Cardiol. 2011;108(4):591-8.
52. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol. 2007;50(19):1914-31.
53. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2005;111(2):186-93.
54. Baggiano A, Boldrini M, Martinez-Naharro A, Kotecha T, Petrie A, Rezk T, et al. Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2020;13(1 Pt 1):69-80.
55. Antoni G, Lubberink M, Estrada S, Axelsson J, Carlson K, Lindsjö L, et al. In Vivo Visualization of Amyloid Deposits in the Heart with 11C-PIB and PET. Journal of Nuclear Medicine. 2013;54(2):213-20.
56. Genovesi D, Vergaro G, Giorgetti A, Marzullo P, Scipioni M, Santarelli MF, et al. [18F]-Florbetaben PET/CT for Differential Diagnosis Among Cardiac Immunoglobulin Light Chain, Transthyretin Amyloidosis, and Mimicking Conditions. JACC Cardiovasc Imaging. 2021;14(1):246-55.

57. Ehman EC, El-Sady MS, Kijewski MF, Khor YM, Jacob S, Ruberg FL, et al. Early Detection of Multiorgan Light-Chain Amyloidosis by Whole-Body (18)F-Florbetapir PET/CT. J Nucl Med. 2019;60(9):1234-9.
58. Hotta M, Minamimoto R, Awaya T, Hiroe M, Okazaki O, Hiroi Y. Radionuclide Imaging of Cardiac Amyloidosis and Sarcoidosis: Roles and Characteristics of Various Tracers. RadioGraphics. 2020;40(7):2029-41.
59. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Annals of Neurology. 2004;55(3):306-19.
60. Minamimoto R, Awaya T, Iwama K, Hotta M, Nakajima K, Hirai R, et al. Significance of 11C-PIB PET/CT in cardiac amyloidosis compared with 99mTc-aprotinin scintigraphy: A pilot study. Journal of Nuclear Cardiology. 2020;27(1):202-9.
61. Ezawa N, Katoh N, Oguchi K, Yoshinaga T, Yazaki M, Sekijima Y. Visualization of multiple organ amyloid involvement in systemic amyloidosis using 11C-PiB PET imaging. European Journal of Nuclear Medicine and Molecular Imaging. 2018;45(3):452-61.
62. Lee SP, Lee ES, Choi H, Im HJ, Koh Y, Lee MH, et al. 11C-Pittsburgh B PET imaging in cardiac amyloidosis. JACC Cardiovasc Imaging. 2015;8(1):50-9.
63. Cuddy SAM, Bravo PE, Falk RH, El-Sady S, Kijewski MF, Park MA, et al. Improved Quantification of Cardiac Amyloid Burden in Systemic Light Chain Amyloidosis: Redefining Early Disease? JACC Cardiovasc Imaging. 2020;13(6):1325-36.
64. Sharpley FA, Fontana M, Martinez-Naharro A, Manwani R, Mahmood S, Sachchithanantham S, et al. Cardiac biomarkers are prognostic in systemic light chain amyloidosis with no cardiac involvement by standard criteria. Haematologica. 2020;105(5):1405-13.
65. Hawkins PN, Lavender JP, Pepys MB. Evaluation of Systemic Amyloidosis by Scintigraphy with 123I-Labeled Serum Amyloid P Component. New England Journal of Medicine. 1990;323(8):508-13.
66. Hazenberg BPC, van Rijswijk MH, Piers DA, Lub-de Hooge MN, Vellenga E, Haagsma EB, et al. Diagnostic Performance of 123I-Labeled Serum Amyloid P Component Scintigraphy in Patients with Amyloidosis. The American Journal of Medicine. 2006;119(4):355.e15-.e24.
67. Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. JACC Cardiovasc Imaging. 2011;4(6):659-70.
68. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol. 2005;46(6):1076-84.
69. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. 99mTc-Pyrophosphate Scintigraphy for Differentiating Light-Chain Cardiac Amyloidosis From the Transthyretin-Related Familial and Senile Cardiac Amyloidoses. Circulation: Cardiovascular Imaging. 2013;6(2):195-201.
70. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12.
71. Mohty D, Petitalot V, Magne J, Fadel BM, Boulogne C, Rouabhia D, et al. Left atrial function in patients with light chain amyloidosis: A transthoracic 3D speckle tracking imaging study. Journal of Cardiology. 2018;71(4):419-27.

72. Dubrey SW, Cha K, Skinner M, Lavalley M, Falk RH. Familial and primary (AL) cardiac amyloidosis: echocardiographically similar diseases with distinctly different clinical outcomes. Heart. 1997;78(1):74-82.
73. Liao R, Jain M, Teller P, Connors LH, Ngoy S, Skinner M, et al. Infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts. Circulation. 2001;104(14):1594-7.
74. Diomede L, Rognoni P, Lavatelli F, Romeo M, del Favero E, Cantù L, et al. A Caenorhabditis elegans-based assay recognizes immunoglobulin light chains causing heart amyloidosis. Blood. 2014;123(23):3543-52.
75. McWilliams-Koeppen HP, Foster JS, Hackenbrack N, Ramirez-Alvarado M, Donohoe D, Williams A, et al. Light Chain Amyloid Fibrils Cause Metabolic Dysfunction in Human Cardiomyocytes. PLoS One. 2015;10(9):e0137716.
76. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circ Res. 2004;94(8):1008-10.
77. Imperlini E, Gnecchi M, Rognoni P, Sabidò E, Ciuffreda MC, Palladini G, et al. Proteotoxicity in cardiac amyloidosis: amyloidogenic light chains affect the levels of intracellular proteins in human heart cells. Sci Rep. 2017;7(1):15661.
78. Shi J, Guan J, Jiang B, Brenner DA, Del Monte F, Ward JE, et al. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway. Proc Natl Acad Sci U S A. 2010;107(9):4188-93.
79. Mishra S, Guan J, Plovie E, Seldin DC, Connors LH, Merlini G, et al. Human amyloidogenic light chain proteins result in cardiac dysfunction, cell death, and early mortality in zebrafish. Am J Physiol Heart Circ Physiol. 2013;305(1):H95-103.
80. Maurer MS, Dunnmon P, Fontana M, Quarta CC, Prasad K, Witteles RM, et al. Proposed Cardiac End Points for Clinical Trials in Immunoglobulin Light Chain Amyloidosis: Report From the Amyloidosis Forum Cardiac Working Group. Circulation: Heart Failure. 2022;15(6).
81. Kotecha T, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, et al. Myocardial Edema and Prognosis in Amyloidosis. J Am Coll Cardiol. 2018;71(25):2919-31.
82. Neben-Wittich MA, Wittich CM, Mueller PS, Larson DR, Gertz MA, Edwards WD. Obstructive intramural coronary amyloidosis and myocardial ischemia are common in primary amyloidosis. Am J Med. 2005;118(11):1287.
83. Migrino RQ, Truran S, Gutterman DD, Franco DA, Bright M, Schlundt B, et al. Human microvascular dysfunction and apoptotic injury induced by AL amyloidosis light chain proteins. Am J Physiol Heart Circ Physiol. 2011;301(6):H2305-12.
84. Sorensen J, Harms HJ, Aalen JM, Baron T, Smiseth OA, Flachskampf FA. Myocardial Efficiency: A Fundamental Physiological Concept on the Verge of Clinical Impact. JACC Cardiovasc Imaging. 2020;13(7):1564-76.
85. Clemmensen TS, Soerensen J, Hansson NH, Tolbod LP, Harms HJ, Eiskjær H, et al. Myocardial Oxygen Consumption and Efficiency in Patients With Cardiac Amyloidosis. Journal of the American Heart Association. 2018;7(21).
86. Dorbala S, Vangala D, Bruyere J, Jr., Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. JACC Heart Fail. 2014;2(4):358-67.

87. Harms HJ, Clemmensen T, Rosengren S, Tolbod L, Pilebro B, Wikstrom G, et al. Association of Right Ventricular Myocardial Blood Flow With Pulmonary Pressures and Outcome in Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2023;16(9):1193-204.
88. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. New England Journal of Medicine. 2021;385(1):46-58.
89. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, Landau H, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26(11):2317-25.
90. Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007;357(11):1083-93.
91. Sharpley FA, Petrie A, Mahmood S, Sachchithanantham S, Lachmann HJ, Gillmore JD, et al. A 24-year experience of autologous stem cell transplantation for light chain amyloidosis patients in the United Kingdom. Br J Haematol. 2019;187(5):642-52.
92. Sidiqi MH, Aljama MA, Buadi FK, Warsame RM, Lacy MQ, Dispenzieri A, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. J Clin Oncol. 2018;36(13):1323-9.
93. Gustine JN, Staron A, Szalat RE, Mendelson LM, Joshi T, Ruberg FL, et al. Predictors of hematologic response and survival with stem cell transplantation in AL amyloidosis: A 25-year longitudinal study. American Journal of Hematology. 2022;97(9):1189-99.
94. D'Souza A, Dispenzieri A, Wirk B, Zhang M-J, Huang J, Gertz MA, et al. Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study. Journal of Clinical Oncology. 2015;33(32):3741-9.
95. Gertz MA, Lacy MQ, Dispenzieri A, Kumar SK, Dingli D, Leung N, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplant. 2013;48(4):557-61.
96. Sanchorawala V, Boccadoro M, Gertz M, Hegenbart U, Kastritis E, Landau H, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid. 2022;29(1):1-7.
97. Hwa YL, Kumar SK, Gertz MA, Lacy MQ, Buadi FK, Kourelis TV, et al. Induction therapy pre-autologous stem cell transplantation in immunoglobulin light chain amyloidosis: a retrospective evaluation. Am J Hematol. 2016;91(10):984-8.
98. Afrough A, Saliba RM, Hamdi A, Honhar M, Varma A, Cornelison AM, et al. Impact of Induction Therapy on the Outcome of Immunoglobulin Light Chain Amyloidosis after Autologous Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation. 2018;24(11):2197-203.
99. Huang X, Wang Q, Chen W, Zeng C, Chen Z, Gong D, et al. Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of renal AL amyloidosis: a randomized controlled trial. BMC Med. 2014;12:2.

100. Manwani R, Hegenbart U, Mahmood S, Sachchithanantham S, Kyriakou C, Yong K, et al. Deferred autologous stem cell transplantation in systemic AL amyloidosis. Blood Cancer J. 2018;8(11):101.
101. Venner CP, Gillmore JD, Sachchithanantham S, Mahmood S, Lane T, Foard D, et al. Stringent patient selection improves outcomes in systemic light-chain amyloidosis after autologous stem cell transplantation in the upfront and relapsed setting. Haematologica. 2014;99(12):e260-3.
102. Munshi PN, Vesole D, Jurczyszyn A, Zaucha JM, St. Martin A, Davila O, et al. Age no bar: A CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma. Cancer. 2020;126(23):5077-87.
103. Pawlyn C, Cairns D, Menzies T, Jones J, Jenner M, Cook G, et al. Autologous stem cell transplantation is safe and effective for fit, older myeloma patients: exploratory results from the Myeloma XI trial. Haematologica. 2020;107(1):231-42.
104. Basset M, Milani P, Foli A, Nuvolone M, Benvenuti P, Nanci M, et al. Early cardiac response is possible in stage IIIb cardiac AL amyloidosis and is associated with prolonged survival. Blood. 2022;140(18):1964-71.
105. Manwani R, Foard D, Mahmood S, Sachchithanantham S, Lane T, Quarta C, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica. 2018;103(4):e165-e8.
106. Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015;126(5):612-5.
107. Gustine JN, Staron A, Mendelson L, Joshi T, Gopal DM, Siddiqi OK, et al. Predictors of treatment response and survival outcomes in patients with advanced cardiac AL amyloidosis. Blood Adv. 2023;7(20):6080-91.
108. Bézard M, Oghina S, Vitiello D, Kharoubi M, Kordeli E, Galat A, et al. Dexamethasone is associated with early deaths in light chain amyloidosis patients with severe cardiac involvement. PLOS ONE. 2021;16(9):e0257189.
109. Palladini G, Merlini G. How I treat AL amyloidosis. Blood. 2022;139(19):2918-30.
110. Chakraborty R, Rosenbaum C, Kaur G, Bhutani D, Radhakrishnan J, Mapara MY, et al. First report of outcomes in patients with stage IIIb AL amyloidosis treated with Dara–VCD front-line therapy. British Journal of Haematology. 2023;201(5):913-6.
111. Oubari S, Hegenbart U, Schoder R, Steinhardt M, Papathanasiou M, Rassaf T, et al. Daratumumab in first-line treatment of patients with light chain amyloidosis and Mayo stage IIIb improves treatment response and overall survival. Haematologica. 2023.
112. Edwards CV, Rao N, Bhutani D, Mapara M, Radhakrishnan J, Shames S, et al. Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood. 2021;138(25):2632-41.
113. Gertz MA, Cohen AD, Comenzo RL, Kastritis E, Landau HJ, Libby EN, et al. Birtamimab plus standard of care in light-chain amyloidosis: the phase 3 randomized placebo-controlled VITAL trial. Blood. 2023;142(14):1208-18.
114. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22(18):3751-7.

115. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30(9):989-95.
116. Kumar SK, Gertz MA, Dispenzieri A. Validation of Mayo Clinic Staging System for Light Chain Amyloidosis With High-Sensitivity Troponin. J Clin Oncol. 2019;37(2):171-3.
117. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013;121(17):3420-7.
118. Muchtar E, Therneau TM, Larson DR, Gertz MA, Lacy MQ, Buadi FK, et al. Comparative analysis of staging systems in AL amyloidosis. Leukemia. 2019;33(3):811-4.
119. Kumar S, Dispenzieri A, Katzmann JA, Larson DR, Colby CL, Lacy MQ, et al. Serum immunoglobulin free light-chain measurement in primary amyloidosis: prognostic value and correlations with clinical features. Blood. 2010;116(24):5126-9.
120. Sidiqi MH, Aljama MA, Muchtar E, Buadi FK, Warsame R, Lacy MQ, et al. Light chain type predicts organ involvement and survival in AL amyloidosis patients receiving stem cell transplantation. Blood Adv. 2018;2(7):769-76.
121. Milani P, Basset M, Russo F, Foli A, Merlini G, Palladini G. Patients with light-chain amyloidosis and low free light-chain burden have distinct clinical features and outcome. Blood. 2017;130(5):625-31.
122. Dittrich T, Bochtler T, Kimmich C, Becker N, Jauch A, Goldschmidt H, et al. AL amyloidosis patients with low amyloidogenic free light chain levels at first diagnosis have an excellent prognosis. Blood. 2017;130(5):632-42.
123. Bochtler T, Hegenbart U, Cremer FW, Heiss C, Benner A, Hose D, et al. Evaluation of the cytogenetic aberration pattern in amyloid light chain amyloidosis as compared with monoclonal gammopathy of undetermined significance reveals common pathways of karyotypic instability. Blood. 2008;111(9):4700-5.
124. Muchtar E, Dispenzieri A, Kumar SK, Ketterling RP, Dingli D, Lacy MQ, et al. Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. Leukemia. 2017;31(7):1562-9.
125. Dumas B, Yameen H, Sarosiek S, Sloan JM, Sanchorawala V. Presence of t(11;14) in AL amyloidosis as a marker of response when treated with a bortezomib-based regimen. Amyloid. 2020;27(4):244-9.
126. Bochtler T, Hegenbart U, Kunz C, Granzow M, Benner A, Seckinger A, et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. J Clin Oncol. 2015;33(12):1371-8.
127. Bochtler T, Hegenbart U, Kunz C, Benner A, Kimmich C, Seckinger A, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. Blood. 2016;128(4):594-602.
128. Bal S, Estrada-Merly N, Costa LJ, Qazilbash MH, Kumar S, D'Souza A. Outcomes of t(11;14) light chain (AL) amyloidosis after autologous stem cell transplantation: benchmark for new therapies. Blood Cancer J. 2023;13(1):170.
129. Fotiou D, Theodorakakou F, Gavriatopoulou M, Migkou M, Malandrakis P, Ntanasis-Stathopoulos I, et al. Prognostic impact of translocation t(11;14) and of other cytogenetic abnormalities in patients with AL amyloidosis in the era of contemporary therapies. European Journal of Haematology. 2023;111(2):271-8.

130. Premkumar VJ, Lentzsch S, Pan S, Bhutani D, Richter J, Jagannath S, et al. Venetoclax induces deep hematologic remissions in t(11;14) relapsed/refractory AL amyloidosis. Blood Cancer Journal. 2021;11(1).
131. Kumar S, Dispenzieri A, Bhutani D, Gertz M, Wechalekar A, Palladini G, et al. Impact of cytogenetic abnormalities on treatment outcomes in patients with amyloid light-chain amyloidosis: subanalyses from the ANDROMEDA study. Amyloid. 2023;30(3):268-78.
132. Bochtler T, Hegenbart U, Kunz C, Benner A, Seckinger A, Dietrich S, et al. Gain of chromosome 1q21 is an independent adverse prognostic factor in light chain amyloidosis patients treated with melphalan/dexamethasone. Amyloid. 2014;21(1):9-17.
133. Aurich M, Bucur J, Vey JA, Greiner S, Aus Dem Siepen F, Hegenbart U, et al. Prognosis of light chain amyloidosis: a multivariable analysis for survival prediction in patients with cardiac involvement proven by endomyocardial biopsy. Open Heart. 2023;10(2):e002310.
134. Cohen OC, Ismael A, Pawarova B, Manwani R, Ravichandran S, Law S, et al. Longitudinal strain is an independent predictor of survival and response to therapy in patients with systemic AL amyloidosis. Eur Heart J. 2022;43(4):333-41.
135. Lee Chuy K, Drill E, Yang JC, Landau H, Hassoun H, Nahhas O, et al. Incremental Value of Global Longitudinal Strain for Predicting Survival in Patients With Advanced AL Amyloidosis. JACC CardioOncol. 2020;2(2):223-31.
136. Milani P, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R, et al. Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis. Circ Cardiovasc Imaging. 2018;11(5):e006588.
137. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, et al. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. J Am Coll Cardiol. 2012;60(12):1067-76.
138. Bodez D, Ternacle J, Guellich A, Galat A, Lim P, Radu C, et al. Prognostic value of right ventricular systolic function in cardiac amyloidosis. Amyloid. 2016;23(3):158-67.
139. Knight DS, Zumbo G, Barcella W, Steeden JA, Muthurangu V, Martinez-Naharro A, et al. Cardiac Structural and Functional Consequences of Amyloid Deposition by Cardiac Magnetic Resonance and Echocardiography and Their Prognostic Roles. JACC Cardiovasc Imaging. 2019;12(5):823-33.
140. Tendler A, Helmke S, Teruya S, Alvarez J, Maurer MS. The myocardial contraction fraction is superior to ejection fraction in predicting survival in patients with AL cardiac amyloidosis. Amyloid. 2015;22(1):61-6.
141. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012;30(36):4541-9.
142. Girnius S, Seldin DC, Cibeira MT, Sanchorawala V. New hematologic response criteria predict survival in patients with immunoglobulin light chain amyloidosis treated with high-dose melphalan and autologous stem-cell transplantation. J Clin Oncol. 2013;31(21):2749-50.
143. Kumar SK, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, et al. Changes in serum-free light chain rather than intact monoclonal immunoglobulin levels predicts outcome following therapy in primary amyloidosis. Am J Hematol. 2011;86(3):251-5.

144. Tandon N, Sidana S, Dispenzieri A, Gertz MA, Lacy MQ, Dingli D, et al. Impact of involved free light chain (FLC) levels in patients achieving normal FLC ratio after initial therapy in light chain amyloidosis (AL). Am J Hematol. 2018;93(1):17-22.
145. Muchtar E, Dispenzieri A, Leung N, Lacy MQ, Buadi FK, Dingli D, et al. Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. Leukemia. 2018;32(10):2240-9.
146. Manwani R, Cohen O, Sharpley F, Mahmood S, Sachchithanantham S, Foard D, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019;134(25):2271-80.
147. Sidana S, Dispenzieri A, Murray DL, Go RS, Buadi FK, Lacy MQ, et al. Revisiting complete response in light chain amyloidosis. Leukemia. 2020;34(5):1472-5.
148. Milani P, Basset M, Nuvolone M, Benigna F, Rodigari L, Lavatelli F, et al. Indicators of profound hematologic response in AL amyloidosis: complete response remains the goal of therapy. Blood Cancer J. 2020;10(8):90.
149. Wechalekar AD, Cibeira MT, Gibbs SD, Jaccard A, Kumar S, Merlini G, et al. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. Amyloid. 2023;30(1):3-17.
150. Sidana S, Muchtar E, Sidiqi MH, Jevremovic D, Dispenzieri A, Gonsalves W, et al. Impact of minimal residual negativity using next generation flow cytometry on outcomes in light chain amyloidosis. Am J Hematol. 2020;95(5):497-502.
151. Sidiqi MH, Aljama MA, Jevremovic D, Muchtar E, Buadi FK, Warsame R, et al. Prognostic Significance of Stringent Complete Response after Stem Cell Transplantation in Immunoglobulin Light Chain Amyloidosis. Biol Blood Marrow Transplant. 2018;24(11):2360-4.
152. Muchtar E, Dispenzieri A, Jevremovic D, Dingli D, Buadi FK, Lacy MQ, et al. Survival impact of achieving minimal residual negativity by multi-parametric flow cytometry in AL amyloidosis. Amyloid. 2020;27(1):13-6.
153. Dispenzieri A, Arendt B, Dasari S, Kohlhagen M, Kourelis T, Kumar SK, et al. Blood mass spectrometry detects residual disease better than standard techniques in light-chain amyloidosis. Blood Cancer J. 2020;10(2):20.
154. Muchtar E, Dispenzieri A, Wisniowski B, Palladini G, Milani P, Merlini G, et al. Graded Cardiac Response Criteria for Patients With Systemic Light Chain Amyloidosis. Journal of Clinical Oncology. 2023;41(7):1393-403.
155. Sidana S, Milani P, Binder M, Basset M, Tandon N, Foli A, et al. A validated composite organ and hematologic response model for early assessment of treatment outcomes in light chain amyloidosis. Blood Cancer J. 2020;10(4):41.
156. Salinaro F, Meier-Ewert HK, Miller EJ, Pandey S, Sanchorawala V, Berk JL, et al. Longitudinal systolic strain, cardiac function improvement, and survival following treatment of light-chain (AL) cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2017;18(9):1057-64.
157. Martinez-Naharro A, Patel R, Kotecha T, Karia N, Ioannou A, Petrie A, et al. Cardiovascular magnetic resonance in light-chain amyloidosis to guide treatment. Eur Heart J. 2022;43(45):4722-35.
158. Pan JA, Kerwin MJ, Salerno M. Native T1 Mapping, Extracellular Volume Mapping, and Late Gadolinium Enhancement in Cardiac Amyloidosis: A Meta-Analysis. JACC Cardiovasc Imaging. 2020;13(6):1299-310.
159. Hansson NH, Sorensen J, Harms HJ, Kim WY, Nielsen R, Tolbod LP, et al. Myocardial Oxygen Consumption and Efficiency in Aortic Valve Stenosis Patients With and Without Heart Failure. J Am Heart Assoc. 2017;6(2).

160. Harms HJ, Hansson NHS, Kero T, Baron T, Tolbod LP, Kim WY, et al. Automatic calculation of myocardial external efficiency using a single (11)C-acetate PET scan. J Nucl Cardiol. 2018;25(6):1937-44.
161. Pilebro B, Arvidsson S, Lindqvist P, Sundstrom T, Westermark P, Antoni G, et al. Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR). J Nucl Cardiol. 2018;25(1):240-8.
162. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;16:129.
163. Kidoh M, Oda S, Takashio S, Kawano Y, Hayashi H, Morita K, et al. Cardiac MRI-derived Extracellular Volume Fraction versus Myocardium-to-Lumen R1 Ratio at Postcontrast T1 Mapping for Detecting Cardiac Amyloidosis. Radiol Cardiothorac Imaging. 2023;5(2):e220327.
164. Briasoulis A, Lama N, Rempakos A, Theodorakakou F, Stamatelopoulos K, Dimopoulos MA, et al. Diagnostic and Prognostic Value of Non-late Gadolinium Enhancement Cardiac Magnetic Resonance Parameters in Cardiac Amyloidosis. Curr Probl Cardiol. 2023;48(4):101573.
165. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-77.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 2012

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-521524

ACTA UNIVERSITATIS
UPSALIENSIS
2024