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## Survey concerning internal medicine physicians and prolonged QT interval: Knowledge and treatment practices

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### Abstract

Prolongation of the QT interval is associated with adverse cardiac events specifically Torsades de pointes (TdP). There are multiple mediations that have a known, possible, or conditional risk for prolonged QT interval, but general practitioners' knowledge of these medications is unknown. We conducted a survey to assess internal medicine (IM) providers' knowledge of risk factors and medications associated with prolonged QT as well as provider experience and comfort when treating patients with prolonged QT. A 17-question, anonymous survey was constructed in 2019 and distributed to IM providers and residents at a tertiary care center. Questions included demographic information, 6 Likert-scale questions gauging provider experience with prolonged QT, and 10 multiple choice clinical vignettes to assess clinical knowledge. Data was analyzed descriptively. Knowledge was assessed *via* clinical vignettes and compared by level of training. Forty-one responses were received out of a total of 87 possible respondents (47.1% response rate). About 70% of respondents see patients with acquired prolonged QT once monthly or more. 95% rarely see congenital prolonged QT. When presented with QTc drug issues, 73% of providers seldom or sometimes consulted pharmacy, but about half used online resources. The average correct score on the clinical vignettes was 5.59/10, with the highest scores seen in attending physicians in their first five years of practice (6.96/10). Our survey suggests that IM providers commonly encounter QT prolonging drugs. Educational efforts to improve knowledge of drug and patient risk factors for TdP may be needed.

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**Core Tip:** Knowledge of drugs that prolong the QTc interval and patient risk factors varies significantly among internal medicine physicians and trainees.

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## INTRODUCTION

In 1966 Dessertenne<sup>[1]</sup> first described the electrocardiogram (ECG) morphology of a ventricular tachycardia that had a peculiar undulating or twisting appearance which he termed Torsades de pointes (TdP). In the over 50 years since this paper was published drug-induced TdP, which may be fatal, has been described for numerous drugs. Indeed, in past years drug induced TdP has been a cause of boxed warnings by the FDA as well as the withdrawal of several drugs from the United States market<sup>[2]</sup>. One of the leading markers of drug induced TdP is the prolonging of the QT interval on the ECG. This measurement (reported in milliseconds) is corrected *via* formula to account for heart rate and is often used as a harbinger of increasing TdP risk<sup>[3-4]</sup>. With their training in pharmacology and its application to the bedside, pharmacists are often sought out for their opinion on the appropriateness of QTc prolonging medication and often seek to counsel prescribers on the risk of drug induced TdP, often by assessment of drug-drug interactions<sup>[5]</sup>. Despite this resource little is known of the background knowledge and attitudes of groups of physicians regarding QTc prolonging medications, especially in various stages of their training. To explore this we designed and administered a survey that aimed to determine the knowledge and attitudes of attending physicians and physician trainees.

## METHODS

A 17-question, anonymous survey was jointly constructed by an internal medicine (IM) physician, a clinical cardiologist and clinical pharmacist. This survey was distributed in 2019 using Qualtrics ([www.qualtrics.com](http://www.qualtrics.com), Qualtrics XM, Seattle, WA, United States). Questions included demographic information, 6 Likert-scale questions gauging provider exposure and comfort with their knowledge of prolonged QT, and 10 multiple choice clinical vignettes. The clinical vignettes covered knowledge of risk factors and medications that prolonged QT as well as treatment of congenital and acquired prolonged QT. This survey was distributed *via* an email invitation to all IM providers and residents as well as psychiatry providers and residents at a tertiary care center in the Midwest. Data was analyzed by evaluating trends and using means to determine provider comfort with prolonged QT identification and treatment. Knowledge was assessed by clinical vignettes and compared by level of training. After data analysis, psychiatry providers and residents were excluded from final data analysis due to low response rate. Descriptive statistics were used in this study. Our Institutional Review Board exempted this study.

## RESULTS

After excluding 4 responses from psychiatric staff and residents, a total of 87 surveys were sent of which 41 responses were received [41 responses out of a total of 87 possible respondents (47.1% response rate)]. This included 18/52 IM providers and



23/35 IM residents. **Table 1** lists the characteristics of our cohort, and **Table 2** lists abbreviated responses to select survey questions. Only 2 respondents reported never having seen patients taking QT prolonging medications; while 17/41 (27%) providers saw such patients weekly or daily. However, 95% participants reported rarely seeing patients with congenital prolonged QT. When presented with patient care issues surrounding prolonged QT, 71% (29/41) of providers seldom or sometimes consulted pharmacy, 99% seldom or never consulted cardiology, and ~50% sometimes used online resources. Thirty-four percent (14/41) reported consulting online resources weekly or daily. We gave examples of types of online resources, but did not ask which types respondents used. The average number correct on the clinical vignettes was 5.59/10 (56%), with the highest scores seen in attending physicians in their first five years of practice [mean 6.96/10 (69%)]. There were no statistically significant differences between the correct responses on the clinical vignettes based on level of training. However, in general, attending physicians generally seemed more familiar with medications prolonging QT while residents were more familiar with patient risk factors prolonging QT.

## DISCUSSION

Drug induced QT prolongation can be a harbinger of the TdP which can be lethal. As more drugs enter the market with the propensity to cause QTc prolongation, the chances for a serious cardiac adverse reaction in patients also increases. This behooves prescribers and pharmacists to be aware of the patient risk factors for TdP, including congenital prolonged QT syndrome, and the medications which prolong the QTc and increase this risk. To our knowledge this is one of the only reports of a dedicated assessment of this subject in general IM physicians and their trainees. A previous report from 2005 from the U.S. is similar to ours surveyed a variety of health care practitioners who attended Grand Rounds Conferences at 12 hospitals<sup>[6]</sup>. In this 20 question survey the median number of correct answers from respondents was 10 (50%) which is similar to our outcomes. This survey also included a problem having respondents manually measure a QTc and found that only 43% did so correctly. Although our survey did not repeat this measure we did find that roughly similar numbers in the knowledge assessment of QTc prolongation. Congenital Long QT syndrome is somewhat rare with a prevalence of 1/2500 live births<sup>[7]</sup>. It may be less surprising then that our respondents did not encounter it frequently. Somewhat more surprising was the relatively low level of pharmacist consultation indicated by our survey. Our health system is a large tertiary teaching hospital where pharmacy services are decentralized and well established. Perhaps the relatively high use of online resources may explain this finding. Certainly, we feel our findings suggest that an educational activity to discuss QT prolonging drugs, and patient risk factors for TdP may be a worthwhile effort given the low scores on our vignettes. Our study has some limitations, chief of which is the small sample size. However, we did receive a high number of overall responses. Also, we only surveyed IM physicians and trainees in our health-system. The application of this information to other geographic areas or other subspecialties of medicine is unknown. Finally although an academic clinical pharmacist and a staff cardiologist designed the vignettes it is possible that errors in designing or writing these problems led to respondents choosing the incorrect answer.

## CONCLUSION

Our survey indicates that our IM physicians often encounter patients receiving QT prolonging medications. They only occasionally consult clinical pharmacists for this problem and use online resources at least half the time. The results of the vignettes suggest a knowledge gap concerning these issues that we plan to address with an interdisciplinary educational program. It would be worthwhile to repeat this study in a larger academic institution to obtain a larger sample size and consider sampling other specialties such as family medicine and psychiatry.

Table 1 Survey participant level of training

Training status	n (%)
PGY-1	12 (29.2)
PGY-2	6 (13.3)
PGY-3	6 (13.3)
Attending physician	17 (37.7)

Table 2 Abbreviated responses to select survey questions

Question	Never, n (%)	Seldom, n (%)	Sometimes, n (%)	Often, n (%)	Daily, n (%)
See patients with QTc prolonging drug	2 (4.4)	11 (29.2)	15 (33.3)	10 (22.2)	2 (4.4)
See patients with congenital long QT	20 (44.4)	19 (46.3)	1 (2.2%)	1 (2.2)	0
Consult pharmacy	11 (24.4)	16 (44.4)	13 (28.8)	1 (2.2)	0
Consult cardiology	20 (44.4)	21 (49.0)	0	0	0
Consult online reference	1 (2.2)	8 (17.7)	18 (43.9)	10 (22.2)	4 (8.8)

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## Retrospective Cohort Study

## Remote monitoring of implantable defibrillators is associated with fewer inappropriate shocks and reduced time to medical assessment in a remote and rural area

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## Abstract

**BACKGROUND**

Implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy with defibrillators (CRT-D) reduce mortality in certain cardiac patient populations. However, inappropriate shocks pose a problem, having both adverse physical and psychological effects on the patient. The advances in device technology now allow remote monitoring (RM) of devices to replace clinic follow up appointments. This allows real time data to be analysed and actioned and this may improve patient care.

**AIM**

To determine if RM in patients with an ICD is associated with fewer inappropriate shocks and reduced time to medical assessment.

**METHODS**

This was a single centre, retrospective observational study, involving 156 patients implanted with an ICD or CRT-D, followed up for 2 years post implant. Both appropriate and inappropriate shocks were recorded along with cause for inappropriate shocks and time to medical assessment.

**RESULTS**

RM was associated with fewer inappropriate shocks (13.6% clinic vs 3.9% RM;  $P = 0.030$ ) and a reduced time to medical assessment ( $15.1 \pm 6.8$  vs  $1.0 \pm 0.0$  d;  $P < 0.001$ ).

**CONCLUSION**

RM in patients with an ICD is associated with improved patient outcomes.

**Key Words:** Implantable cardioverter defibrillator; Inappropriate shocks; Remote



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**Core Tip:** Advances in device technology now allow remote monitoring of implantable cardioverter defibrillators to replace clinic follow up appointments. This allows real time data to be analysed and actioned. This study shows that remote monitoring of such devices is associated with fewer inappropriate shocks and reduced time to medical assessment in a remote and rural area. This represents better patient care and will reduce the morbidity caused by inappropriate shocks.

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## INTRODUCTION

Implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy with defibrillation (CRT-D) are established treatments for a range of cardiac disorders and are proven to reduce mortality<sup>[1-4]</sup>. The continuing care for patients with ICDs and CRT-Ds involves regular follow up appointments to monitor the function of the device and the clinical status of the patient. A limitation of the conventional clinic follow up model is the lack of information between visits and immediately after therapy (e.g., shocks). Remote monitoring (RM) using a telephonic transmission of pacemaker information from the patients home fills this gap with clinical trials having demonstrated the usefulness<sup>[5,6]</sup> including its safety<sup>[7]</sup>, economic benefits<sup>[8]</sup> and improved clinical outcome<sup>[9]</sup>.

The delivery of a shock can result in adverse effects for the patient, including impaired quality of life, psychiatric disturbances and is associated with increased all cause mortality<sup>[10]</sup>, which increases with each subsequent shock. Shocks can be appropriate (e.g., to treat potentially fatal rapid ventricular rhythms) or inappropriate (non-fatal tachyarrhythmia or lead dysfunction). RM reduces inappropriate shocks<sup>[5,11,12]</sup> through the earlier detection of events preceding the delivery of inappropriate shocks. In addition, RM offers the ability to reduce the time from a clinical event (such as an appropriate or inappropriate shock) to a clinical decision being made [time to medical assessment (TMA)]. This is an especially pertinent issue in remote and rural areas where patients can live long distances from specialist care.

This study aimed to assess appropriate and inappropriate shocks in patients with and without RM and to measure differences in TMA in a real world, remote and rural population.

## MATERIALS AND METHODS

### Study design and population

This was a single site, retrospective observational study in a hospital serving a remote and rural population of 320000 spread over a geographical area of 32500 km<sup>2</sup> including several islands. Patients who were implanted with an ICD or CRT-D between January 1, 2010 and January 1, 2014 were included. All patients were followed up for 2 years post implant. There were no exclusion criteria. Device programming and the use of RM was decided on an individual basis at the discretion of the cardiac rhythm physiologists after discussion with the clinician and patient. All RM systems transmit a variety of parameters, (such as lead parameters, battery status, therapy delivery, arrhythmias, intracardiac electrograms (IEGM), heart rate and rhythm statistics and patient activity levels) from the patients' device *via* a mobile network link of landline, to the manufacturer's central repository. Clinicians responsible for the follow up of

patients receive automated email notifications if pre-specified criteria are met (*e.g.*, shock delivered). All transmitted data is stored on a dedicated, secure, password protected website. Follow up arrangements between groups were similar, and on a case by case basis at the discretion of the follow up clinician. All ad-hoc reviews prompted by events highlighted from home monitoring were also arranged at the discretion of the clinician.

### **Data collection**

Baseline characteristics were collected from patient medical records. Device related data was retrieved from both hard and electronic copies of the patient records and from each of the companies' respective RM systems; Home Monitoring (Biotronik), CareLink (Medtronic) or Merlin (St Jude Medical).

### **TMA**

TMA was calculated in days; beginning with event onset at the delivery of a shock and ending when a clinical decision was made. Clinical decision was defined as management of an event, medical intervention, physician decision, decision for follow up clinic, or hospitalisation.

### **Therapy analysis**

An inappropriate shock was defined as the delivery of a shock not for true ventricular tachycardia or ventricular fibrillation. Shocks were classified on a shock by shock basis, rather than by episode. For example, 4 shocks all received for an episode of T wave over sensing would be counted as 4 shocks not 1. Analysis of the IEGM by cardiac physiologists was used to ascertain whether shocks were appropriate or inappropriate. Inappropriate shocks were classified in relation to their cause, for example, atrial fibrillation (AF) or flutter, supraventricular tachycardia (SVT), T wave over sensing, noise, or V lead displacement.

### **Data handling and statistical analysis**

Patients were defined as "RM" if they had an ICD/RCT-D with RM function and "clinic" if they had a standard ICD/CRT-D with no RM function. Baseline characteristics from the "RM" *vs* "clinic" monitoring groups were compared using the Wilcoxon rank sum test for continuous variables, with the Chi squared test being used for categorical variables. Continuous variables were reported as mean with standard deviation. The Man Whitney *U*, chi squared test and the students *t* test were used to analyse the inappropriate shock and TMA as appropriate. All tests were performed at a  $P = 0.05$  significance level. All data were processed and analysed using Microsoft Excel 2007 software and SPSS software version 18.0.

### **Ethics**

This was a service evaluation using routinely collected data and therefore formal ethical approval was not required. Local Caldecott approval was obtained to access patients' records for this project.

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## **RESULTS**

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### **Baseline characteristics**

Of 156 patients were identified, with 45 in the clinic group and 111 in the RM group. Baseline characteristics are shown in [Table 1](#). There was no significant difference between the two groups except for the manufacturer of the implanted device. A total of 16 patients were lost to follow up (10.3%) ([Table 2](#)).

### **Incidence of shocks**

[Table 2](#) shows the incidence of appropriate and inappropriate shocks for both groups. There was no significant difference between groups for the number of patients receiving appropriate shocks [3 (8.6%) clinic patients *vs* 14 (13.6%) RM patients,  $P = 0.388$ ]. However, there was a significant difference for the number of patients receiving inappropriate shocks [4 (11.4%) clinic patients *vs* 4 (3.9%) RM patients,  $P = 0.030$ ]. The maximum number of shocks received by 1 patient was 14, this patient was in the clinic follow up group and shocks were due to incorrectly identified SVT.

Table 1 Baseline characteristics

	Clinic, n (%)	RM, n (%)
<i>n</i>	45	111
Age at implant (year)	63.6 ± 13.0	64.2 ± 11.5
Male	30 (85.7)	85 (82.5)
NYHA functional class		
I	12 (34.3)	40 (38.8)
II	18 (51.4)	52 (50.5)
III	5 (14.3)	11 (10.7)
Cardiac disease category		
Coronary artery disease	21 (60.0)	54 (52.4)
Non ischaemic dilated cardiomyopathy	4 (11.4)	15 (14.6)
Primary electrical disease	3 (8.6)	5 (4.9)
Hypertrophic cardiomyopathy	1 (2.9)	6 (5.8)
Valvular heart disease	1 (2.9)	2 (1.9)
Hypertensive	1 (2.9)	3 (2.9)
Other cardiomyopathy	1 (2.9)	5 (4.9)
Undetermined	2 (5.7)	10 (9.7)
None	1 (2.9)	1 (1.0)
ECG history of		
Sustained ventricular tachycardia	7 (20.0)	24 (23.3)
Ventricular fibrillation	6 (17.1)	19 (18.4)
Torsade de pointes	1 (2.9)	3 (2.9)
Indication for ICD		
Primary	20 (57.1)	57 (55.3)
Secondary	15 (42.9)	46 (44.7)
Implanted device		
Single chamber ICD	13 (37.1)	27 (26.2)
Dual chamber ICD	19 (54.3)	74 (71.8)
CRT-D	5 (14.3)	23 (22.3)
Type of implant		
Original	30 (85.7)	83 (80.6)
Replacement	5 (14.3)	20 (19.4)
Drug therapy		
Beta-blocker	25 (71.4)	69 (70.0)
Digoxin	2 (5.7)	12 (11.7)
Amiodarone	4 (11.4)	8 (7.8)
Manufacturer		
Biotronik	11 (31.4)	44 (42.7)
Boston scientific/guidant	8 (28.8)	0 (0) <sup>1</sup>
Medtronic	5 (14.3)	41 (39.8)
St Jude Medical	11 (31.4)	18 (17.5)

<sup>1</sup>Boston remote monitoring (latitude) was not available at the time of implant.

RM: Remote monitoring; NYHA: New York Heart Association; ECG: Electrocardiograph; ICD: Implantable cardioverter defibrillator; CRT-D: Cardiac resynchronisation therapy with defibrillators.

**Table 2 Incidence of appropriate and inappropriate shocks and time to medical assessment**

	Clinic, <i>n</i> (%)	RM, <i>n</i> (%)
<i>n</i>	45	111
Reason lost to follow up		
Out of area	3 (6.7)	4 (3.6)
Death	7(15.6)	4 (3.6)
Number of patients receiving shocks (appropriate)	3 (8.6)	14 (13.6)
1 shock	3 (8.6)	9 (8.7)
2-9 shocks	0	6 (5.8)
≥ 10	0	0
Number of patients receiving shocks (inappropriate)	4 (11.4)	4 (3.9)
1 shock	0	2 (1.9)
2-9 shocks	2 (5.7)	2 (1.9)
≥ 10	2 (5.7)	0
Causes inappropriate shocks (number of shocks)		
AF/flutter	18 (42.9)	2 (20.0)
SVT	14 (33.3)	1 (10.0)
T wave over sense	0	1 (10.0)
V lead displacement	0	6 (60.0)
Noise	10 (23.8)	0
TMA		
Appropriate shocks	11.7 ± 9.2	1.8 ± 0.6
Inappropriate shocks	15.1 ± 6.8	1.0 ± 0.0

TMA: Time to medical assessment; RM: Remote monitoring; AF: Atrial fibrillation; SVT: Supraventricular tachycardia.

### **Cause of inappropriate shocks**

The most common cause of inappropriate shocks was AF/flutter in the clinic group and ventricular lead displacement in the RM group (Table 2).

### **TMA**

TMA was significantly higher in clinic *vs* RM group for inappropriate shocks (15.1 ± 6.8 *vs* 1.0 ± 0.0 d; *P* < 0.001) and appropriate shocks (11.7 ± 9.2 *vs* 1.8 ± 0.6 d; *P* < 0.001). (Figure 1) Reasons for a delayed TMA included patients unaware of shocks, ability to travel and delayed transfers from community hospitals.

## **DISCUSSION**

This study has shown that RM is associated with a reduced TMA and a reduced number of inappropriate shocks in a patient population living in a remote and rural area.

Prompt identification and intervention of inappropriate shocks is essential to prevent subsequent inappropriate shocks. Although patients are typically aware of receiving a shock there are occasions when patients are not. This study was able to demonstrate an association between RM and a reduced TMA following the delivery of

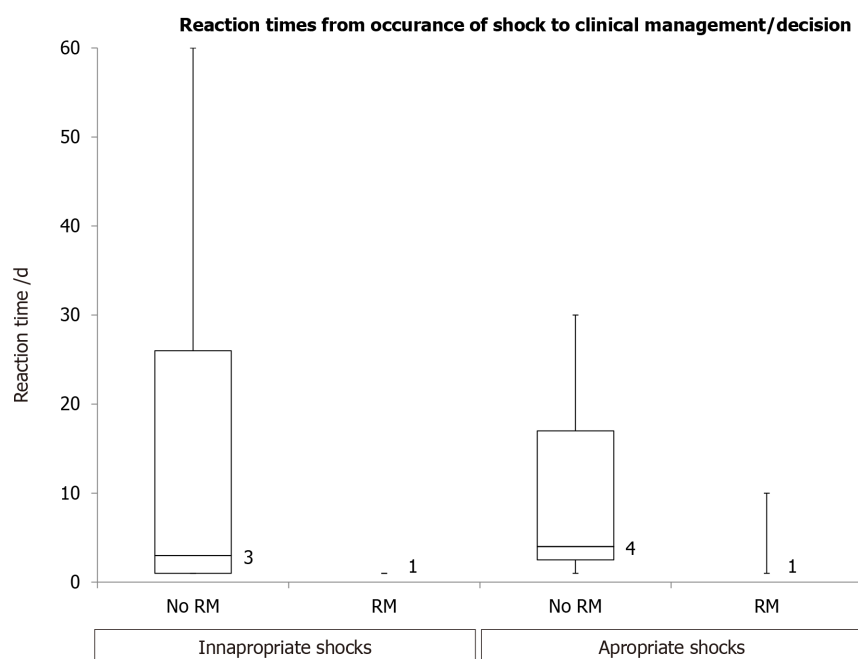


Figure 1 Box-whisker plot for time to medical assessment following a shock. RM: Remote monitoring.

a shock (appropriate or inappropriate) compared to clinic follow up. A quicker TMA following an inappropriate shock may reduce the likelihood of further inappropriate shocks due to medical or programming interventions. Although programming or prescribing changes are not necessarily required after an appropriate shock, RM is associated with a reduced TMA by allowing remote assessment of the device and care to be provided to the patient at local hospitals, with specialist device support provided remotely. The ability of RM to reduce TMA has been demonstrated in larger clinical trials<sup>[13,14]</sup> and the home guide registry<sup>[15]</sup>. However, it is worth noting that these trials included all device alerts when calculating TMA rather than just shock as is the case here. The ability of RM to reduce TMA and to deliver the same level of care to all patients regardless of geographical location is advantageous.

The reduced number of inappropriate shocks in the RM group is consistent with data from the ECOST and EVATEL trials<sup>[11,12]</sup>. ICD shocks are known to have both a physical and psychological effect on the patient, including acute pain, anxiety and depression<sup>[13]</sup>, as well as having an adverse effect on the myocardial function, leading to an increased risk of death<sup>[16,17]</sup>. With these known detrimental effects of shocks it is well recognised that there is a need to reduce the occurrence of inappropriate shocks, in order to increase the quality of life for patients with ICDs and CRT-Ds.

### Comparisons of service

The incidence of inappropriate shocks (all follow up methods) from major clinical trials were compared to the findings in this study. In contemporary trials with clinic follow up inappropriate ICD therapies have been reported in up to 25%-35% of cases<sup>[18-20]</sup>, with more recent trials reporting inappropriate shock rate of 10%-11.5%<sup>[3,21]</sup>, also with clinic follow up. Our study showed an inappropriate shock rate in clinic follow up patients of 11.4%, which is not dissimilar; suggesting that the service patients receive here is comparable to hospitals worldwide. There are fewer trials with inappropriate shock data for patients followed up with RM, but in a recently reported cohort a rate of 3.9% per annum was reported<sup>[22]</sup>, which is identical to the rate in this current study.

### Safety

The safety of RM compared to clinic follow up has been confirmed by several large clinical trials, such as TRUST<sup>[7]</sup> and ECOST<sup>[11]</sup>, both of which have evaluated major adverse events to prove the non-inferiority of RM compared to clinic follow up. However, these trials only included those patients with Biotronik's Home Monitoring system. Although a similar trial by Al-Khatib *et al*<sup>[23]</sup> reported similar findings for Medtronic's Carelink system. Our study included patients with 3 manufacturers (Biotronik, Medtronic, St Jude Medical and Boston scientific/Guidant) with no obvious

differences between the four providers although numbers were small.

### **Limitations**

This was a retrospective single centre study and therefore there is a risk that these results are not generalizable. However, all device follow up in our area is provided at this one site and all device patients were included. Our centre is the only cardiac unit in our region and therefore it is likely that our patient population is representative. A further potential limitation is the study design which was an observational cohort study and not randomised. Nevertheless, the groups although of differing size were similar with regard to demographics and the results are consistent with previous studies. The implant period covered 4 years, with RM perhaps becoming more available/widely adopted in those patients implanted later on in the study and improved experience and medical therapy may have skewed results. The number of inappropriate shocks in both groups is small and this is a statistical limitation of the study. It is also recognised that this study does not include data regarding anti-tachycardia pacing delivered to patients, whilst this would provide additional therapy and arrhythmia information it was out with the scope of this review.

### **Recommendations**

The lower incidence of inappropriate shocks in patients with RM compared to published data is of interest. The geographical location of the study centre in a dispersed population has led to an increase use of RM, perhaps more than other centres and the informal response in terms of staff and patients has been positive.

## **CONCLUSION**

RM was associated with fewer inappropriate shocks and reduced TMA post shock (for appropriate and inappropriate shock). Inappropriate shocks are known to have detrimental effects on a patient's quality of life and to increase mortality. For these reasons it is essential that reducing the incidence of inappropriate shocks is a high priority in the continuing care and follow up of patients. More widespread use of RM might lead to a decrease in inappropriate shocks.

## **ARTICLE HIGHLIGHTS**

### **Research background**

Implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy with defibrillators (CRT-D) reduce mortality in certain cardiac patient populations. However, inappropriate shocks pose a problem, having both adverse physical and psychological effects on the patient. The advances in device technology now allow remote monitoring (RM) of devices to replace clinic follow up appointments. This allows real time data to be analysed and actioned and this may improve patient care.

### **Research motivation**

This is because inappropriate shocks and delayed assessment can lead to morbidity and reduced quality of life for patients.

### **Research objectives**

The primary objective was to determine if RM in patients with an ICD is associated with fewer inappropriate shocks and reduced time to medical assessment.

### **Research methods**

This was a single centre, retrospective observational study, involving 156 patients implanted with an ICD or CRT-D, followed up for 2 years post implant. Both appropriate and inappropriate shocks were recorded along with cause for inappropriate shocks and time to medical assessment.

### **Research results**

RM was associated with fewer inappropriate shocks (13.6% clinic *vs* 3.9% RM;  $P = 0.030$ ) and a reduced time to medical assessment ( $15.1 \pm 6.8$  *vs*  $1.0 \pm 0.0$  d;  $P < 0.001$ ).



**Research conclusions**

RM in patients with an ICD is associated with both improved patient outcomes.

**Research perspectives**

The role of RM in other areas should be investigated.

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Prospective Study

## Elevated interleukin-6 levels are associated with impaired outcome in cardiac transthyretin amyloidosis

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**Author contributions:** Hein SJ was responsible for recruitment of the trial, data acquisition, conducting interleukin-6 measurements and drafted the manuscript; Knoll M was responsible for the statistical analyses of the data; Aus dem Siepen F was involved in recruitment for the trial and substantially revised the manuscript; Furkel J, Schönland S, Hegenbart U and Katus HA substantially revised the manuscript; Kristen AV and Konstandin MH were responsible for the funding, study design and substantially revised the manuscript.

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### Abstract

#### BACKGROUND

Elevated interleukin (IL)-6-levels have been described in familial variant transthyretin amyloidosis (ATTRv) associated polyneuropathy and heart failure. However, IL-6 in cardiac ATTR amyloidosis (ATTR-CM) and its prognostic value have not been investigated yet.

#### AIM

We aim to study the correlation between IL-6 levels with clinical presentation (Gillmore-class) and outcome [heart transplantation or death (htx/death)], or the combined endpoint of cardiac decompensation or htx/death in ATTR-CM.

**Institutional review board**

**statement:** The study was reviewed and approved by the ethical review committee Heidelberg (Approval No. S-485-2016).

**Informed consent statement:** All study participants, or their legal guardian, provided written consent prior to study enrollment.

**Conflict-of-interest statement:** Hegenbart U received honoraria of Pfizer, the other authors have nothing to declare.

**Data sharing statement:** No additional data are available.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 checklist, and the manuscript was prepared and revised according to the CONSORT 2010 checklist.

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**METHODS**

IL-6 levels of 106 ATTR-CM patients [54 wild-type ATTRwt, 52 ATTRv-CM], 15 asymptomatic carriers of ATTR mutations (aATTRv-CM) and 27 healthy donors were quantified using Luminex technology. Statistical analysis was performed using parametric survival regression models.

**RESULTS**

We found that IL-6 levels from wild-type ATTR patients were significantly elevated compared to healthy controls, while aATTRv-CM carriers and ATTRv-CM patients did not show a significant difference. IL-6 levels showed significantly higher values in increasing Gillmore classes. Univariate analyses revealed association of low IL-6 levels with cardiac decompensation and htx/death [odds ratio: 0.26 (0.09-0.72),  $P = 0.01$ ] and htx/death [odds ratio: 0.15 (0.04-0.58),  $P = 0.006$ ]. However, in the multivariate model, no significant improvement of risk prediction was seen for IL-6, while established prognostic factors were significantly associated with outcome.

**CONCLUSION**

Raised IL-6 levels correlate with clinical presentation and are associated with worse outcome in ATTR-CM but do not improve stratification in addition to established risk factors.

**Key Words:** Transthyretin amyloidosis; Inflammation; Heart failure; Interleukin-6; Outcome; Risk stratification

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**Core Tip:** This was a monocentric prospective trial with 106 patients suffering from transthyretin cardiomyopathy (ATTR-CM) seeking to evaluate the prognostic value of interleukin-6 in ATTR-CM. Interleukin-6 is associated with outcome in ATTR-CM but did not further ameliorate existing risk prediction models.

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**INTRODUCTION**

Systemic amyloidosis comprises a group of diseases leading to extracellular protein deposition in tissue resulting in organ dysfunction. Depending on the specific type of protein causing misfolding and amyloid formation, different organs are involved. In cardiac amyloidosis, protein deposition in myocardium is most frequently due to amyloid light chain or transthyretin (TTR) deposition<sup>[1]</sup>. In transthyretin cardiac amyloidosis (ATTR), two disease entities are found: Hereditary variant transthyretin amyloidosis (ATTRv) and wild-type transthyretin (ATTRwt) amyloidosis<sup>[2]</sup>. ATTRv results from a point mutation in the TTR gene. Until now, more than 100 different disease causing mutations are known. Depending on the mutation, patients present with leading neurological [familial transthyretin polyneuropathy (ATTRv-PN)] or cardiac symptoms (ATTRv-CM)<sup>[3]</sup>. Furthermore, thanks to increased awareness and also the establishment of new sensitive diagnostic methods, e.g., 99mTc-labelled bone scintigraphy and cardiac MRI, the incidence of ATTR amyloidosis in general and particularly of ATTRwt, has increased over the last years<sup>[4]</sup>. In this disease entity, no mutation in the transthyretin gene is found. ATTRwt mainly affects elderly, predominantly male patients with cardiac symptoms leading. The clinical course of ATTR varies significantly within patients with rapid progression of symptoms, within a few months in some patients, and stable course for many years in others<sup>[2]</sup>. Therefore, early identification of patients at high risk for a more aggressive course of the disease

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is crucial for the preservation of quality of life, exercise capacity and ultimately survival and early initiation of amyloid specific therapies.

In the last years the role of systemic inflammation for progression of cardiovascular disease in general has been established, especially in coronary heart disease. Elevated interleukin (IL)-6 levels are described in patients suffering from heart failure with preserved ejection fraction (HFpEF), atrial fibrillation and elevated N-terminal pro-brain natriuretic peptide (NTproBNP)<sup>[6]</sup>. Furthermore, on a molecular level increased cardiac IL-6 and IL-6 receptor messenger ribonucleic acid (mRNA) levels in myocardial tissue have been associated with worsening of heart failure<sup>[6]</sup>. In animal models of pressure overload and heart failure inhibition of the IL-6 axis was protective<sup>[7]</sup>. In very recent studies, association of inflammation and disease progression could be documented for amyloidosis too. Immunohistochemical detection of lymphocytes, macrophages and cytotoxic cells in cardiac specimen of light-chain amyloidosis (AL) and ATTR amyloidosis patients was associated with impaired outcome<sup>[8]</sup>. Gene expression profiling of peripheral blood leukocytes was valuable for the diagnosis of symptomatic patients with ATTR amyloidosis<sup>[9]</sup>. Moreover, systemic inflammatory state quantified as cytokine panels in patients' blood plasma has been described in hereditary amyloid polyneuropathy<sup>[10,11]</sup>. In patients with ATTR-PN, data are inconsistent as IL-6 levels were found to be unchanged in ATTRv-PN patients and asymptomatic gene carriers compared to healthy controls<sup>[10]</sup>. In another study, increased IL-6 levels were seen in ATTRv-PN patients and asymptomatic mutation carriers as well<sup>[11]</sup>.

Since nothing is known about IL-6 in patients with ATTR-CM to date, the aim of the present study was to quantify the levels of IL-6 in peripheral blood in this cohort and analyze the correlation with clinical presentation and prognosis.

## MATERIALS AND METHODS

### Study population

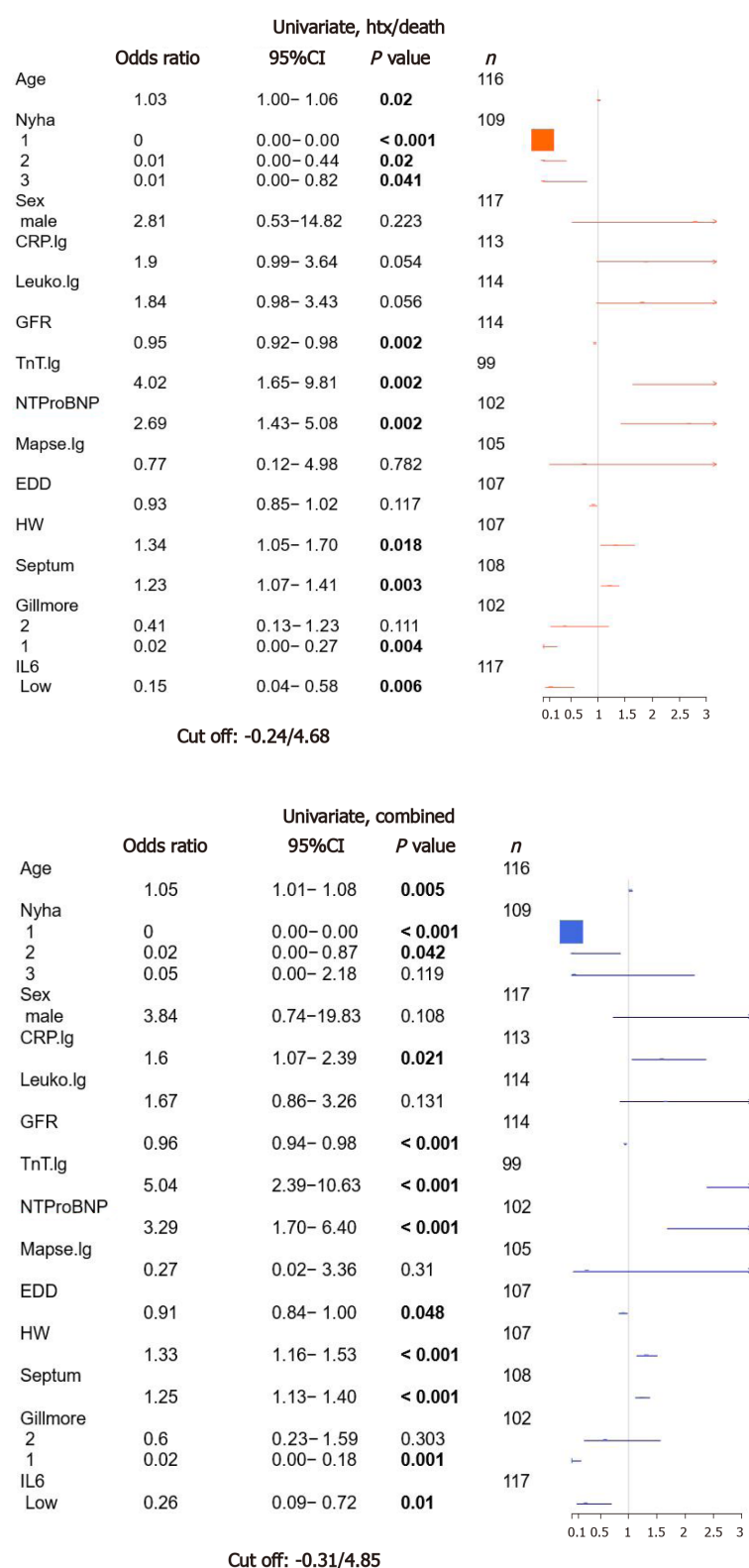
Between July 2016 and October 2018, 138 patients who consecutively presented in our tertiary referral center for amyloidosis at Heidelberg University Hospital were screened and asked to donate blood for this study. One patient declined study participation. Inclusion criteria were age > 18 and < 90 years, diagnosis of ATTRwt, ATTRv or asymptomatic carrier of a mutation causing ATTRv. Patients who suffered from AL amyloidosis ( $n = 7$ ) were excluded due to other pathophysiologic disease mechanism. Patients who underwent liver transplantation ( $n = 1$ ) or diagnosis remained unclear ( $n = 3$ ) were excluded from study participation. Also, patients receiving TTR-lowering therapies ( $n = 5$ ) were excluded due to reduction of disease driving protein. Patients who received TTR-stabilizer therapy, however, were eligible to participate in the study ( $n = 26$ ), as dysfunctional protein is still present. These patients already received tafamidis 20 mg daily at study inclusion for grade 1 ATTR polyneuropathy during the whole follow-up period. Therefore, a total of  $n = 121$  patients were included in the present study and subscribed written informed consent approved by the ethical review committee Heidelberg (S-485-2016), in accordance to the declaration of Helsinki. To attain a control group, healthy volunteers were asked to donate blood, when echocardiography, clinical presentation and biomarkers were normal [high-sensitive troponin T, C-reactive protein (CRP) and NTproBNP] ( $n = 27$ ).

Blood samples were attained with regular venipuncture during the medical visit. Therefore, one additional lithium heparin monovette (4.9 mL, Sarstedt, Nümbrecht, Germany) was collected and plasma was prepared by standard centrifugation. Samples were aliquoted and stored at  $-80^{\circ}\text{C}$ , conditions well established to have no impact upon IL-6 stability<sup>[12,13]</sup>. After the inclusion of the last patient, IL-6 levels of all patients were measured simultaneously.

For subgroup analysis in [Figure 1](#), patients were divided by positive cardiac TroponinT (cTnT) levels according to the estimated cutoff in our recent study<sup>[14]</sup>. For subcohort definition regarding natriuretic peptide levels [glomerular filtration rate (GFR) adjusted NTproBNP], NTproBNP levels were adjusted to renal function as described by Luchner *et al*<sup>[15]</sup>.

Echocardiography was conducted using 2D imaging, M-Mode, Doppler and Strain analyses. Ejection fraction was calculated from 2D echocardiography imaging and diastolic dysfunction was graded in accordance to current guidelines from the American Society of Echocardiography<sup>[16]</sup>. Grade II and higher were considered as significant diastolic dysfunction.





**Figure 1 Univariate analysis for clinical/laboratory/risk score parameters and interleukin-6.** Parametric survival regression, loglogistic distribution, wild-type *P* values. CRP: C-reactive protein; IL6: Interleukin-6; NTProBNP: N-terminal pro-brain natriuretic peptide; GFR: Glomerular filtration rate.

### Follow-up

Endpoint follow-up was performed by interviewing patients directly during outpatient visits or *via* phone call after 12 mo. Additionally, patients' files of subsequent hospitalization due to cardiac decompensation were analyzed. Pre-specified endpoints were heart transplantation or death (htx/death) and a combination of htx/death or cardiac decompensation (major cardiac events, MACE).



### Luminex assay

Plasma concentrations of IL-6 were quantified using the Luminex MAGPIX system (R&D systems, Minneapolis, MN, United States). IL-6 measurements were conducted in adherence to the manufacturer's instructions.

### Statistical analysis

Statistical analyses were conducted using R, v3.6.3<sup>[17]</sup>. IL-6 concentrations were calculated from a standard curve attained by the standards provided by the Luminex kit. Values were fitted using a sigmoidal, three parameter, hill fit equation [ $f = a \cdot x^b / (c^b + x^b)$ ]. For further analysis, log transformed data were used. IL-6 values below the detection level were set to zero ( $n = 1$ ). Measurements were transformed as described in<sup>[18]</sup> prior to log and z-transformation for subsequent analysis.

Time-to-event data were censored after 30 month. Median follow-up data were calculated with survreg using inverted event data. Confidence intervals were computed with the ciTools package<sup>[19]</sup>. Cutoff selection for prognostic stratification of patients (smallest  $P$  values, minimum group size of 10%) was performed with the dataAnalysisMisc package<sup>[20]</sup>. Cutoffs were calculated per endpoint.

Uni- and multivariate survival analyses were performed with parametric survival regression models assuming loglogistic distributed data.

Associations between diagnosis groups and patient characteristics were evaluated using analysis of variance or chi-squared tests for categorical and continuous variables, respectively. Significance level alpha was set to 5% (two-sided).

## RESULTS

### Study population

A total of 121 patients and 27 healthy controls participated in this study. In 50 patients, cardiac amyloidosis was confirmed by myocardial biopsy, 56 patients were diagnosed by specific myocardial storage in 99m-TC-DPD-bone scintigraphy and concomitant serological exclusion of AL amyloidosis. Furthermore, 15 asymptomatic gene carriers were diagnosed by familial history and genotyping. According to the examination results, patients were grouped into ATTRwt ( $n = 54$ ), symptomatic ATTRv-CM ( $n = 52$ ) and asymptomatic aATTRv-CM ( $n = 15$ ).

The ATTRv-CM group consists of patients with mutations at Val30Met ( $n = 18$ ), Val20Ile ( $n = 11$ ), Ile107Val ( $n = 5$ ), Leu58His ( $n = 6$ ), Cys10Arg ( $n = 4$ ), Val122Ile ( $n = 3$ ), Ala45Thr ( $n = 1$ ), Ile84Asn ( $n = 1$ ), Ile107Phe ( $n = 1$ ), Arg34Gly ( $n = 1$ ), Thr126Arg ( $n = 1$ ). Furthermore, the asymptomatic mutation carriers were Val20Ile ( $n = 5$ ), Val30Met ( $n = 6$ ), Val122Ile ( $n = 1$ ), Cys10Arg ( $n = 1$ ), Ile107Val ( $n = 1$ ), Ile84Thr ( $n = 1$ ). **Table 1** presents clinical characteristics of study participants.

ATTRwt patients were significantly older and primarily male patients. Furthermore, treatment with diuretics, beta blockers and angiotensin converting enzyme inhibitors was more common in the ATTRwt group. In electrocardiogram (ECG), atrial fibrillation was more common in ATTRwt patients compared to both other patient groups, and ATTRwt patients presented higher prevalence of bundle branch blocks and were significantly more often equipped with pacemakers. Furthermore, diabetes was more often recorded in their medical history as co-existing diseases. Serologically, ATTRwt patients presented higher cTnT and NTproBNP levels as well as lower GFR compared to both other groups. This resulted in higher clinical risk classes when classification was specified according to Gillmore *et al*<sup>[4]</sup>. In echocardiography, ATTRwt patients presented more pronounced myocardial hypertrophy and lower ejection fraction than patients from the two other groups.

During the recruitment period of the study, Tafamidis was only approved for ATTRv patients with concomitant polyneuropathy; therefore, treatment with Tafamidis was significantly more frequent in the ATTRv group. IL-6 levels did not show significant differences in patients treated with Tafamidis (**Supplementary Figure 1**). New York Heart Association (NYHA) class was higher in ATTRwt. All other variables tested (body mass index, antihypertensive medication, times in the ECG and echocardiographic parameters) were not significantly different between groups.

### IL-6 is elevated in ATTRwt patients and rising with Gillmore class in ATTR-CM patients

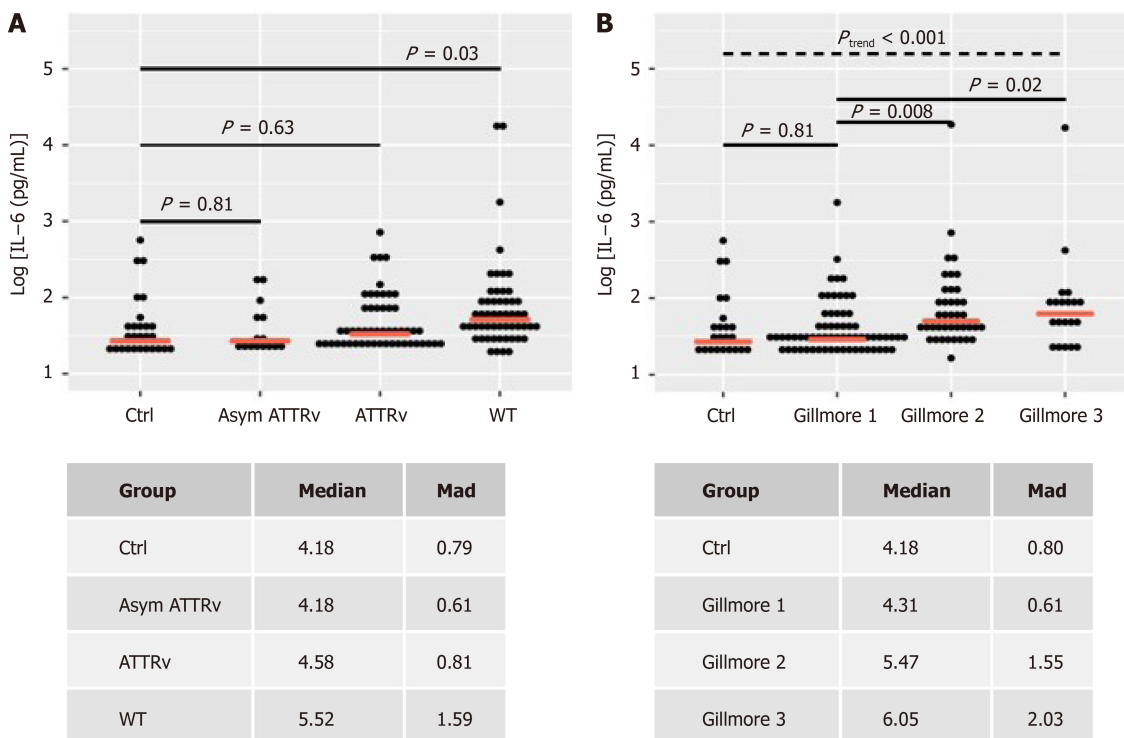
In healthy controls, median IL-6 level was 4.18 pg/mL (median absolute deviation (mad): 0.8) and in aATTRv-CM IL-6 was 4.18 (0.61) pg/mL as well (**Figure 2A**).

Table 1 Patient characteristics

Study population, <i>n</i> = 148	Asympt ATTRv, <i>n</i> = 15	ATTRv, <i>n</i> = 52	Ctrl, <i>n</i> = 27	ATTRwt, <i>n</i> = 54	<i>P</i> value
Age (yr)	46.9 ± 11.2	66.1 ± 8.1	53.3 ± 19.6	78.5 ± 6.8	< 0.001
Sex, <i>n</i> (%)					
Male	9 (60.0)	39 (75.0)	16 (59.3)	49 (90.7)	< 0.001
Female	6 (40.0)	13 (25.0)	11 (40.7)	5 (9.3)	
BMI	27.3 ± 5.6	26.1 ± 4.9	26.0 ± 5.5	25.5 ± 3.0	0.59
Medication, <i>n</i> (%)					
Tafamidis	0 (0)	25 (48.1)	0 (0)	1 (1.9)	< 0.001
Beta blocker	2 (13.3)	20 (38.5)	7 (25.9)	41 (75.9)	< 0.001
ACE inhibitors/ AT1 antagonists	3 (25.0)	16 (30.8)	7 (25.9)	37 (68.5)	< 0.001
Diuretics	2 (13.3)	27 (51.9)	4 (14.8)	52 (96.3)	< 0.001
Other antihypertensive medication (amlodipin, doxacor, nitrendipin)	2 (13.3)	1 (1.9)	0 (0)	7 (13.0)	0.10
Functional impairment					
Karnofsky performance index, <i>n</i> (%)					< 0.001
≥ 80	15 (100)	39 (75.0)	27 (100)	45 (83.3)	
< 80	0 (0.0)	13 (25.0)	0 (0)	9 (16.7)	
NYHA class, <i>n</i> (%)					< 0.001
I	15 (100)	23 (44.2)	23 (85.2)	7 (12.9)	
II	0 (0.0)	15 (28.8)	3 (11.1)	16 (29.6)	
III/IV	0 (0.0)	14 (26.9)	1 (3.7)	31 (57.4)	
Risk classification, <i>n</i> (%)					
Gillmore					< 0.001
I	15 (100)	30 (57.7)		16 (29.6)	
II	0 (0.0)	14 (26.9)		26 (48.1)	
III	0 (0.0)	8 (15.4)		12 (22.2)	
Medical history, <i>n</i> (%)					
Pacemaker implantation	0 (0.0)	10 (19.2)	1 (3.7)	13 (24.0)	0.03
Diabetes mellitus	0 (0.0)	3 (5.7)	0 (0)	9 (16.7)	0.02
Atrial fibrillation	1 (6.7)	16 (30.8)	3 (11.1)	35 (64.8)	< 0.001
ECG findings					
Number of bundle branch blocks	0.14 ± 0.36	0.70 ± 0.85	0.19 ± 0.49	1.1 ± 0.8	< 0.001
Sinus rhythm, <i>n</i> (%)	14 (93.3)	37 (71.2)	24 (88.9)	26 (48.1)	< 0.001
Pace maker rhythm, <i>n</i> (%)	0 (0.0)	4 (7.7)	0 (0)	7 (13.0)	0.11
Low voltage pattern, <i>n</i> (%)	2 (13.3)	9 (17.3)	0 (0)	8 (14.8)	0.18
Heart frequency (bpm)	68.8 ± 14.3	74.2 ± 14.5	69.4 ± 10.6	79.6 ± 13.9	0.006
PQ interval (ms)	142.1 ± 30.1	176.8 ± 39.2	158.3 ± 25.6	210.3 ± 41.9	< 0.001
QRS time (ms)	99.8 ± 16.6	112.7 ± 30.2	97.3 ± 11.4	128.0 ± 33.3	< 0.001
QTc duration (ms)	402.4 ± 15.9	432.8 ± 42.4	400.6 ± 12.5	445.7 ± 32.5	< 0.001
Echocardiography					
Posterior wall (mm)	9.5 ± 1.9	14.0 ± 0.5	10.0 ± 0.3	15.4 ± 3.2	< 0.001

IVS (mm)	10.9 ± 1.9	17.0 ± 0.7	11.0 ± 0.3	19.2 ± 3.9	< 0.001
Ejection fraction (%)	58.7 ± 2.2	52.5 ± 1.4	60.0 ± 1.9	44.3 ± 11.3	< 0.001
Diastolic dysfunction, <i>n</i> (%)	3 (20.0)	40 (76.9)	4 (14.8)	49 (90.7)	< 0.001
Global longitudinal strain	-14.6 ± 14.2	-12.0 ± 0.7		-9.8 ± 4.0	< 0.001
MAPSE (mm)	1.5 ± 0.3	1.1 ± 0.3	1.6 ± 0.09	0.9 ± 0.3	0.09
TAPSE (mm)	2.3 ± 0.4	1.8 ± 0.2	2.1 ± 0.1	1.5 ± 0.6	0.02
Pericardial effusion, <i>n</i> (%)	0 (0.0)	3 (5.8)	0 (0)	6 (11.1)	0.31
PA pressure (mmHg)	26.0 ± 4.1	31.0 ± 1.0	25.0 ± 1.3	35.8 ± 9.8	0.005
<b>Biomarkers</b>					
NtproBNP(ng/L)	173.6 ± 260.6	3457.3 ± 4321.9	258.8 ± 35.2	7219.4 ± 8213.5	< 0.001
hsTNT (pg/mL)	4.7 ± 2.4	59.0 ± 95.4	8.1 ± 7.6	63.6 ± 40.7	< 0.001
GFR (mL/min)	101.1 ± 14.6	75.9 ± 24.9	96.3 ± 22.1	55.8 ± 18.6	< 0.001

ACE: Angiotensin converting enzyme; AT1: Angiotensin type 1; ATTRv: Variant transthyretin amyloidosis; ATTRwt: Wild-type transthyretin amyloidosis; BMI: Body mass index; NtproBNP: N-terminal pro-brain natriuretic peptide; ECG: Electrocardiogram; GFR: Glomerular filtration rate; IVS: Intravenous sedation; MAPSE: Mitral annular plane systolic excursion; NYHA: New York Heart Association; TAPSE: Tricuspid annular plane systolic excursion; TNT: TroponinT.



**Figure 2** Interleukin-6 values are depicted according to study group or Gillmore class. A: Study group; B: Gillmore class. Ctrl: Control group; asym ATTRv: Asymptomatic ATTRv; ATTRv: Symptomatic ATTRv amyloidosis; WT: Wild-type ATTR amyloidosis. Linear model *P* values for two-group comparisons and trend-test (Jonckheere-Terpstra). Median and median absolute deviation (mad) of non-log and non-z transformed data (pg/mL). Red dashed line: Median interleukin-6 value per group.

Symptomatic patients with hereditary ATTRv-CM showed slightly increased levels of IL-6 with 4.58 pg/mL (0.81) not reaching significance ( $P = 0.63$ ). In contrast, ATTRwt patients showed significant increased median IL-6 levels compared to controls [5.52pg/mL (1.59),  $P = 0.03$ ]. IL-6 levels showed an increase from control and Gillmore class 1 to Gillmore classes 2 and 3 (trend-test,  $P < 0.001$ ). Median IL-6 levels were significantly increased in Gillmore 2 and 3 *vs* Gillmore 1 (Figure 2B).

**IL-6 is associated with cardiovascular events in ATTR-CM**

IL-6 levels were analyzed using parametric survival models to identify best separating cutoffs for the prognostic separation of patients for both evaluated endpoints. For death/htx endpoint, a cutoff of -0.24, corresponding to 4.68 pg/mL was identified (low:  $n = 78$ ; high:  $n = 70$ ).

For MACE, a cutoff of -0.31, corresponding to 4.85 pg/mL, was identified (low:  $n = 72$ ; high:  $n = 76$ ). For 117 of 148 patients (79%), follow-up after index event was available. Median follow-up was 13.5 [95% confidence interval (CI): 11.6-15.7] months for death/htx and 13.6 (95%CI: 11.7-15.9) months for MACE.

During follow-up period, 19 patients died, six were listed for high urgent heart transplantation, two died waiting for the organ and two patients were successfully transplanted. Fourteen patients were hospitalized due to cardiac decompensation requiring additional treatment with diuretics for recompensation. Twenty-four patients reached at least one of the prespecified combined endpoints. Patients with increased IL-6 levels had a higher risk for MACE ( $P = 0.01$ ) or death/htx ( $P = 0.006$ ) (Figure 3).

**IL-6 allows improved risk prediction in NTproBNP positive patients and in cTnT negative patients**

Two well established biomarkers for risk stratification in ATTR-CM are cTnT and NTproBNP levels<sup>[21-23]</sup>. Therefore, we repeated our risk assessment for patients in these two high-risk subgroups. In patients with low NTproBNP levels, no prespecified endpoint was observed during follow-up. In patients with elevated NTproBNP levels (above 450 ng/mL<sup>[24-26]</sup>), high IL-6 levels were significantly associated htx/death ( $P = 0.01$ ) and a clear trend for increased incidence of MACE could be observed ( $P = 0.052$ ). Dividing our cohort according to the established cutoff for cTnT of 50 ng/mL identified in the groups with cTnT negative group a prognostic separation for death/htx endpoint ( $P = 0.02$ ) and a borderline significant prognostic separation for MACE ( $P = 0.049$ ). In the cTnT negative group no significant prognostic separation was found (Figure 4).

**IL-6 is no independent risk predictor in ATTR-CM**

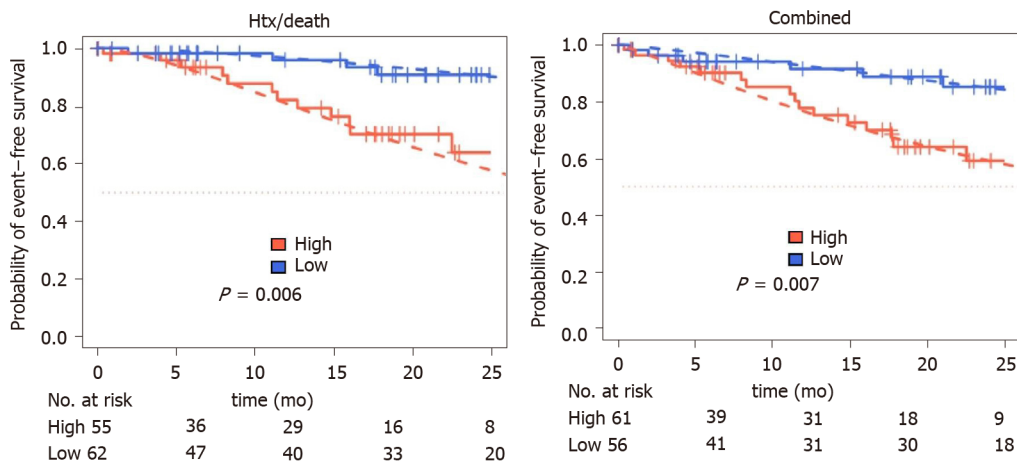
To estimate the value of IL-6 for the prespecified endpoints htx/death as well as MACE, we performed an univariate survival analysis for established risk parameters as age, NYHA classification, gender, GFR, echocardiographic parameters (mitral annular plane systolic excursion, end diastolic diameter, septum thickness, estimated heart weight) and Gillmore class and biomarkers (cTnT, NTproBNP). Furthermore inflammatory markers as CRP and leukocyte count were included as well as IL-6. As shown in Figure 1, age, NYHA class, GFR, cTnT, NTproBNP, heart weight, septum thickness, Gillmore class and IL-6 showed significant association with htx/death. The same characteristics were also significantly associated with MACE, but also CRP levels and EDD showed a significant correlation with MACE. The odds ratio (OR) for low IL-6 and htx/death was 0.15 ( $P = 0.006$ ), and for MACE, OR of low *vs* high IL-6 was 0.26 ( $P = 0.01$ ).

To test for independent risk prediction of IL-6, a multivariate analysis was calculated including IL-6 and all other parameters significant in the univariate model except for the combined feature Gillmore. However, in the multivariate model, IL-6 did not improve risk stratification, neither for htx/death [OR: 0.42; 95%CI (0.06-2.83);  $P = 0.37$ ] nor MACE [OR: 1.11; 95%CI (0.23-5.29);  $P = 0.89$ ] (Supplementary Figure 2).

**DISCUSSION**

In the present monocentric prospective study, elevated IL-6 levels were found in patients with ATTRwt amyloidosis but not aATTRv-CM carriers or ATTRv-CM patients. IL-6 concentrations correlated with severity of clinical presentation as quantified in the Gillmore classification. Furthermore, IL-6 levels were significantly associated with clinical outcome as death/htx or MACE in the univariate analysis. However, in the multivariate analysis IL-6 did not show a significant additional value over established risk predictors.

Elevated IL-6 levels have been described in amyloid A (AA) amyloidosis and ATTRv-PN. AA amyloidosis is a secondary amyloidosis in chronic inflammatory diseases (e.g., rheumatoid arthritis)<sup>[27]</sup>. In these patients, application of the human monoclonal antibody tocilizumab directed against the IL-6 receptor induced rapid



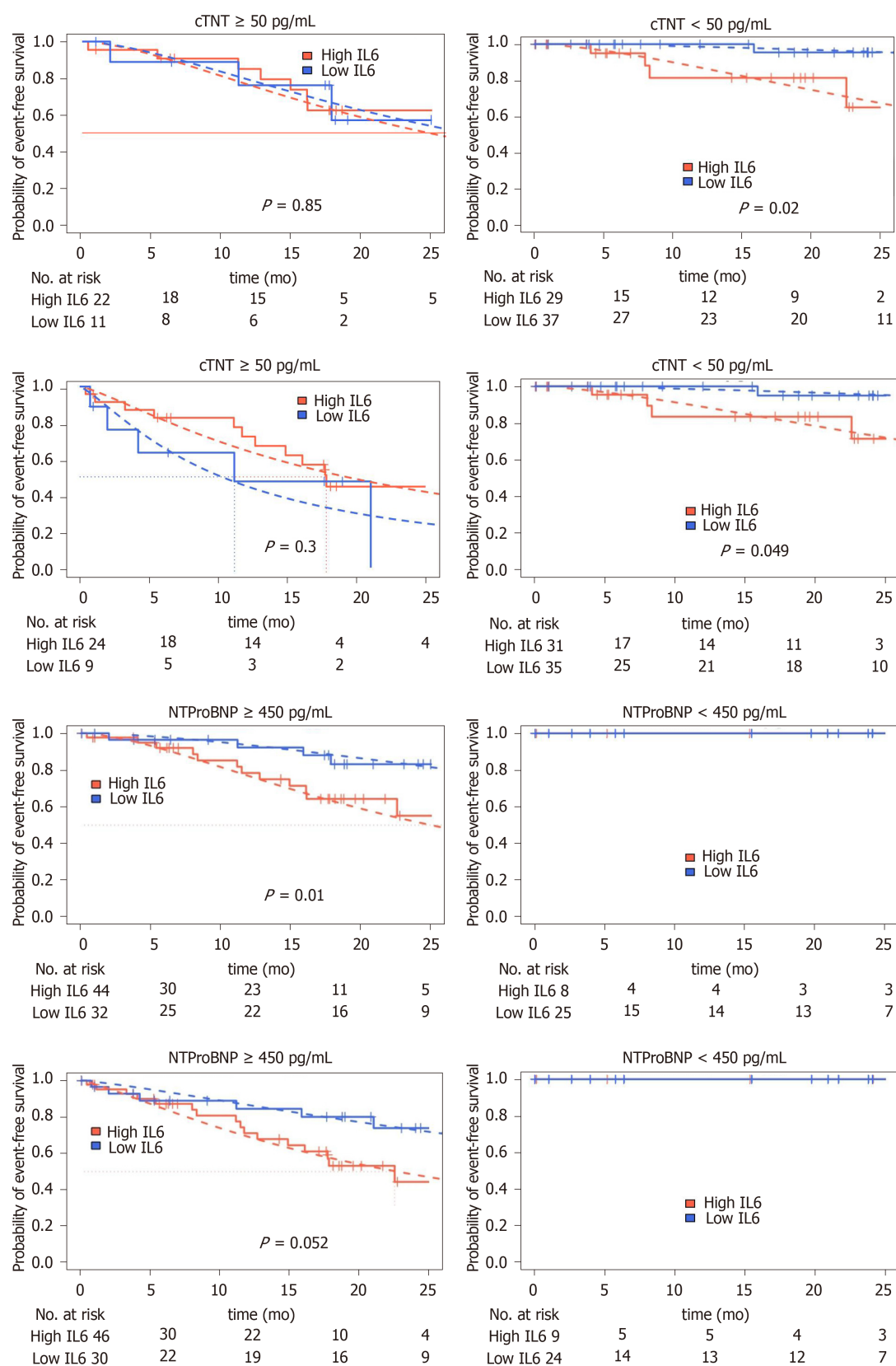
**Figure 3 Kaplan-Meier curves for combined, decompensation and death or heart transplantation endpoints for dichotomized interleukin-6.** Dashed: Parametric survival regression (log logistic distribution), wild-type *P* values.

clinical improvement without influencing the amyloid deposits<sup>[28,29]</sup>. Therefore, for AA-amyloidosis the IL-6 axis is known to be causally involved in the pathogenesis of the inflammatory disease. In contrast, for ATTRv-PN data are inconsistent: Increased IL-6 levels were found independent from clinical presentation: Asymptomatic mutation carriers as well as symptomatic ATTRv-PN patients show increased IL-6 levels<sup>[11]</sup>. On the other hand no differences for IL-6 were seen in the study by Azevedo *et al*<sup>[10]</sup> in the same cohort. These data suggest that mutated TTR might be able to evoke an inflammatory state but not sufficient to establish the disease. Therefore, other factors have to be present, which are not identified yet. In contrast, in our cardiac cohort ATTRwt patients show elevated IL-6 levels, however, aATTRv-CM carriers or ATTRv-CM patients did not. Therefore, in patients with preferentially cardiac manifestation of ATTR amyloidosis, IL-6 rather seems to be secondary to the manifestation of the disease as sign of heart failure but not preceding the organ affection and, therefore, not causing the manifestation in the first hand.

In the large BIOSTAT-CHF cohort (*n* = 2329 patients) IL-6 levels were elevated in patients with heart failure and HFpEF, atrial fibrillation or elevated NTproBNP levels<sup>[5]</sup>. These clinical findings are often present in ATTR-cardiomyopathy patients as well. During the last years new diagnostic methods and novel therapeutic approaches raised awareness for ATTR cardiomyopathy enabling differentiation between cardiac amyloidosis and HFpEF from other reasons. On a molecular basis, activation of the IL-6 axis is known to induce concentric hypertrophy and diastolic dysfunction in rats, which might contribute to the pathology in ATTR-CM<sup>[30]</sup>. In line with these data, a correlation of IL-6 levels with clinical severity and prognosis of ATTR-CM could be observed in the herein project; however, in the multivariate analysis including well established risk factors no additional value was seen in the IL-6 quantification. Therefore, IL-6 rather seems to be a factor associated with heart failure irrespective of the underlying disease.

## CONCLUSION

Taken together, raised IL-6 levels correlate with clinical presentation and are associated with worse outcome in ATTR-CM, but do not improve stratification in addition to established risk factors. Since molecular animal studies suggest a contribution of IL-6 to the manifestation of heart failure and pathological remodeling<sup>[7,31]</sup>, a study interfering with the IL-6 axis is needed to prove this concept in patients with heart failure in general and ATTR-CM amyloidosis specifically. Our data show an association to severity and prognosis of the disease; evidence for causality in the pathogenesis cannot be provided here. Since the multivariate analysis did not show a significant association, further research is needed to improve risk stratification.



**Figure 4** Kaplan-Meier curves for combined, decompensation and death or heart transplantation endpoints for dichotomized interleukin-6 in N-terminal pro-brain natriuretic peptide and TroponinT stratified patients. Dashed: Parametric survival regression (loglogistic distribution), likelihood ratio  $P$  values. cTNT: cardiac TroponinT; IL6: Interleukin-6; NTProBNP: N-terminal pro-brain natriuretic peptide.



## ARTICLE HIGHLIGHTS

### Research background

In transthyretin cardiac amyloidosis (ATTR), protein deposition leads to myocardial thickening and heart failure, which is defined as ATTR cardiomyopathy (ATTR-CM). Recently, evidence was raised that inflammation might be associated with disease progression in ATTR polyneuropathy and heart failure. But until now little is known about the inflammatory state in ATTR-CM. Therefore, we measured IL-6 levels in ATTR-CM and analyzed its predictive value for cardiac outcome.

### Research motivation

In ATTR-CM stable disease over several years as well as rapidly progressive disease courses are described. This discrepancy might result from differences in immunological response to myocardial protein deposits in ATTR-CM.

### Research objectives

The objective of the study was to investigate differences in IL-6 levels and evaluate its predictive value for cardiovascular outcome (death/heart transplantation, decompensation or a combined endpoint).

### Research methods

In this monocentric prospective study, 106 ATTR-CM patients were included, and IL-6 levels were measured using Luminex technology. Follow-up period was 12 mo, and statistical analysis was performed using parametric survival regression models.

### Research results

IL-6 is associated with outcome in ATTR-CM but does not improve risk stratification in addition to established risk prediction parameters. The study thereby provides evidence that IL-6 axis might be involved in the pathogenesis of ATTR-CM. To investigate this hypothesis further, additional studies are needed.

### Research conclusions

The study showed that IL-6 is associated with outcome in ATTR-CM but does not add further risk stratification potential to established risk prediction models.

### Research perspectives

Further studies are needed to investigate inflammatory response in ATTR-CM.

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