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Rapid Fire Abstract Session: News on Phenotyping and Risk Stratification in Acute and Chronic Heart Failure

O56–O63

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O56

Activity of the adrenomedullin system to personalize post-discharge treatment in acute heart failure

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Objectives: Activity of the adrenomedullin system was quantified by using bioactive-adrenomedullin (bio-ADM), the biologically active moiety, and midregional proadrenomedullin (MR-proADM), a prohormone fragment, to 1) identify acute heart failure (AHF) phenotypes with disproportional benefit or harm from specific treatments at hospital discharge, 2) predict mortality, and 3) compare the prognostic utility of both biomarkers.

Methods: This prospective multicentre study using central adjudication of AHF measured bio-ADM in all patients and MR-proADM in a predefined subgroup in a blinded fashion on admission. Both biomarkers were measured at discharge as well. Interaction with specific treatments at hospital discharge and the biomarkers' prognostic utility during 365 days' follow-up were assessed.

Results: Among 1,886 patients with adjudicated AHF, 514 patients (27.3%) died during the 365 days' follow-up. Patients with bio-ADM plasma concentrations above the median were at a much higher risk of death (HR 1.87, 95% CI 1.57-2.24; p <0.001). After adjusting for age, creatinine plasma concentrations, and medical treatment at discharge, those patients derived disproportional benefit if treated with diuretics and/or angiotensin-converting-enzyme inhibitors/angiotensin receptor blocker (interaction p-values <0.05). These findings were confirmed only for the diuretics treatment when quantifying the adrenomedullin system using MR-proADM plasma concentrations (n = 764). For predicting mortality, both biomarkers performed well and

Figure: O56-1.

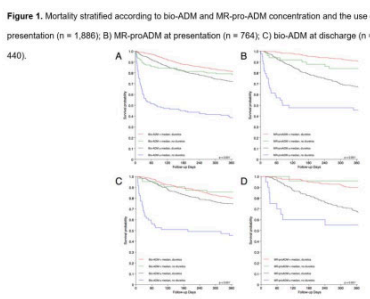

Figure 1. Mortality stratified according to bio-ADM and MR-pro-ADM concentration and the use of diuretics on discharge: A) bio-ADM at presentation (n = 1,886); B) MR-proADM at presentation (n = 764); C) bio-ADM at discharge (n = 1,001); D) MR-proADM at discharge (n = 440).

bio-ADM: bioactive adrenomedullin. MR-proADM: midregional proadrenomedullin.

MR-proADM had a higher predictive accuracy as compared to bio-ADM (p <0.001).

Conclusion: Quantifying the activity of the adrenomedullin system helps to personalize post-discharge treatment and risk-prediction in AHF.

O57

Association of echocardiographic progression and genetic profile in arrhythmogenic right ventricular cardiomyopathy

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is frequently associated with mutations in genes coding for desmosomal proteins. In this study, we investigated the association of genetic status with ARVC progression as defined by echocardiographic parameters.

Methods: We tested 62 ARVC patients for their genetic profile. Accordingly, they were grouped in mutation positive (48 (77%) patients; median age 48.5 years; 33 (69%) males), and mutation negative (14 (23%) patients; median age 45 years; 10 (71%) males). Prevalent mutations were Desmoglein-2 (DSG2) in 16 (26%), Desmoplakin (DSP) in 14 (23%), and Plakophilin-2 (PKP2) in 9 (15%) patients.

Table O57-1. Baseline and follow-up echocardiographic findings of study subjects. * significant results.

Parameters	Geno-Positive: Baseline mean (SD)	Geno-Positive: follow-up mean (SD)	Sig.	Geno-Negative: baseline mean (SD)	Geno-Negative: follow-up mean (SD)	Sig.
Tricuspid annular plane systolic excursion	19.1 (±5.1)	18.2 (±5.4)	0.24	21.3 (±5.2)	20.6 (±3.8)	0.77
Fractional area change	32.8 (±10.9)	29.9 (±9.9)	0.09	34.6 (±12.3)	35.3 (±8.7)	0.79
Left ventricular ejection fraction	56.5 (±9.8)	52.7 (±11.9)	0.01 *	60.3 (±7.5)	57.9 (±4.3)	0.32
Right ventricular end-diastolic area	30.2 (±9.7)	32.8 (±10.7)	0.002 *	25.6 (±6.5)	28.6 (±7.2)	0.1
Left atrium diameter	3.5 (±0.5)	3.7 (±0.6)	0.014 *	4.2 (±0.8)	4 (±0.6)	0.61
Right atrium short diameter	4.1 (±0.8)	4.6 (±1.3)	0.008 *	4.5 (±1.3)	4.3 (±0.6)	0.72
Right atrium long diameter	4.9 (±0.7)	5.4 (±1.1)	0.002 *	5.7 (±0.7)	5.6 (±0.8)	0.92

Results: At baseline, there were no significant differences in clinical characteristics between the two groups. Patients were followed-up for a median time period of 1420 days, and there was no significant difference in the duration of follow-up between the two groups (p = 0.05).

In the mutation positive group, there was a significant increase in right ventricular end-diastolic area (p = 0.002), right atrial short (p = 0.008) and long (p = 0.002) diameter, left atrial diameter (p = 0.014), and a decrease in left ventricular ejection fraction (p = 0.014) during follow up. Right ventricular functial parameters did not change significantly (tricuspid annular plane systolic excursion: p = 0.24; fractional area change: p = 0.088).

In the mutation negative group, none of the aforementioned echocardiographic findings exhibited any significant difference during follow-up: right ventricular end-diastolic area (p = 0.1); right atrial short (p = 0.7) and long (p = 0.9) diameter, left atrial diameter (p = 0.6), and left ventricular ejection fraction (p = 0.3). Similarly, right ventricular functional parameters did not change significantly (tricuspid annular plane systolic excursion: p = 0.77; fractional area change: p = 0.80. Results are summarized in the table O57-1.

Conclusions: There is a strong association between echocardiographic progression of ARVC phenotype and the presence of a pathogenic mutation. Such mutations should be searched in all patients with an ARVC phenotype, and mutation positive individuals should be followed-up in shorter intervals.

O58

Relative hypochromia and mortality in acute heart failure

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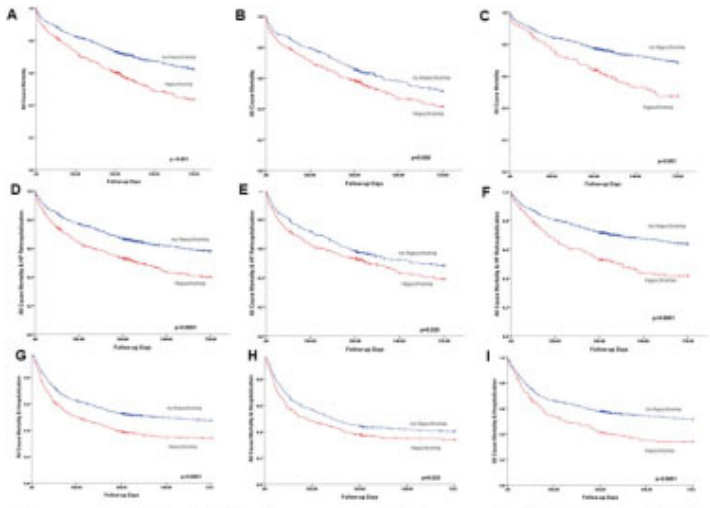
Introduction: Relative hypochromia of erythrocytes defined as a reduced mean corpuscular hemoglobin concentration (MCHC) is a surrogate of iron deficiency. We aimed to evaluate the prevalence and prognostic impact of relative hypochromia in acute heart failure (AHF).

Methods: We prospectively characterized 1574 patients presenting with an adjudicated diagnosis of AHF to the emergency department. Relative hypochromia was defined as a MCHC ≤ 330g/L and determined at presentation. The presence of AHF was adjudicated by two independent car-

Figure: O58-1.



Cumulative all-cause mortality (A-C), all-cause mortality or acute heart failure (AHF) rehospitalization (D-F) and all-cause mortality or all-cause rehospitalization (G-I) according to relative hypochromia in patients with acute heart failure (AHF)

diologists. All-cause mortality and AHF-rehospitalization were the primary prognostic end-points.

Results: Overall, 455 (29%) AHF patients had relative hypochromia. Patients with relative hypochromia had higher hemodynamic cardiac stress as quantified by NT-proBNP concentrations (p<0.001), more extensive cardiomyocyte injury as quantified by high-sensitive cardiac troponin T (hs-cTnT) concentrations (p <0.001), and lower estimated glomerular filtration rate (eGFR; p<0.001) as compared to AHF patients without hypochromia. Cumulative incidence for all-cause mortality and AHF-rehospitalization at 720-days were 50% and 55% in patients with relative hypochromia as compared to 33% and 39% in patients without hypochromia, respectively (both p <0.0001). The association between relative hypochromia and increased mortality (HR 1.7, 95% CI 1.4-2-0) persisted after adjusting for anemia (HR 1.5, 95% CI 1.3-1.8), and after adjusting for hemodynamic cardiac stress (HR 1.46, 95% CI 1.21-1.76) and eGFR (HR 1.5, 95% CI 1.3-1.8, p <0.001).

Conclusions: Relative hypochromia is common and a strong and independent predictor of increased mortality in AHF. Given the direct link to diagnostic (endoscopy) and therapeutic interventions to treat functional iron deficiency, relative hypochromia deserves increased attention as an inexpensive and universally available biomarker.

O59

Genotype-phenotype correlations in patients with arrhythmogenic cardiomyopathy: results from next generation sequencing in a large multicenter cohort

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Introduction: This study aims to identify genotype-phenotype correlations in a multicenter cohort of patients with arrhythmogenic cardiomyopathy (ACM) using clinical exome analysis by next-generation sequencing (NGS).

Methods and Results: Clinical data from 186 unrelated patients with ACM from the Swiss and Chinese ACM cohorts were prospectively studied. NGS covering at least 66 genes being associated with cardiomyopathies/channelopathies was applied to identify pathogenic variants. Genetic variants were identified in 96 (52%) patients. Multivariable Cox regression revealed non-desmosomal variants and multigenic variants both as independent risk factors of heart transplantation (HR2.285, 0.014 and HR3.496, 0.048, respectively), whereas plakophilin-2 (*PKP2*) variants were a significant risk factor of major arrhythmic cardiac events (MACE, HR3.190, 0.001). Genotype-positive patients exhibited a lower MACE free survival (0.032) and survival free from the composite end-point (heart transplantation and MACE; 0.011) as compared to genotype-negative patients. Patients with non-desmosomal variants had a lower heart transplant free survival as compared to those with desmosomal variants (0.005). Patients with desmoplakin (*DSP*) or desmoglein-2 (*DSG2*)/desmocollin-2 (*DSC2*) variants had a lower heart transplant free survival than those with *PKP2* variants (0.025).

Conclusions: ACM patients with specific variants have distinct clinical characteristics and outcomes. *PKP2* confers a strong arrhythmogenic phenotype, whereas *DSP* variants, multigenic variants, and non-desmosomal variants put the patients at risk for left ventricular involvement and heart transplantation.

O60

Quantifying hemodynamic cardiac stress and cardiomyocyte injury in hypertensive and normotensive acute heart failure

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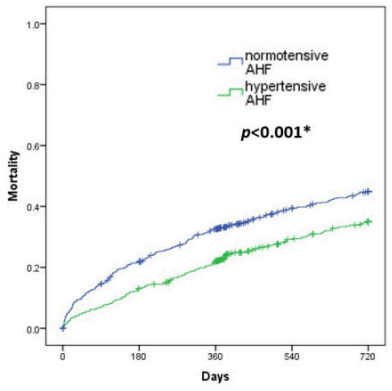
Introduction: Better characterization of the different pathophysiological mechanisms involved in normotensive and hypertensive acute heart failure (AHF) might help to develop novel individualized treatment strategies.

Methods: The extent of hemodynamic cardiac stress and cardiomyocyte injury was quantified by measuring B-type natriuretic peptide (BNP) as well as high-sensitive cardiac troponin T (hs-cTnT) in 1,152 unselected patients presenting with AHF to the emergency department (derivation cohort). Systolic blood pressure (SBP) of 90 - 140 mmHg at presentation was used to define normotensive AHF. Findings regarding hemodynamic cardiac stress and cardiomyocyte injury were validated in a second independent AHF cohort (validation cohort; n = 324).

Results: In the derivation cohort 667 (58%) patients had hypertensive AHF. Hemodynamic cardiac stress, as quantified by BNP levels, was significantly higher in normotensive AHF as compared to hypertensive AHF (1,105 pg/mL versus 827 pg/mL, p <0.001). In addition, the extent of cardiomyocyte injury, as quantified by hs-cTnT, was significantly higher in normotensive AHF as compared to hypertensive AHF (41 ng/L versus 33 ng/L, p <0.001). These findings were confirmed in the validation cohort.

Figure: O60-1.



Cumulative mortality in hypertensive and normotensive AHF
*Log-rank test at 360 days and 720 days
AHF = acute heart failure

Conclusion: Biomarker profiling revealed that the extent of hemodynamic stress and cardiomyocyte injury is different in patients with normotensive and hypertensive AHF. This characterization could help to understand AHF phenotypes better, which in turn may lead to more specific management in future, thus improving the dismal prognosis in these patients.

O61

Discharge echocardiographic parameters of RV and LV function but not of changes in cardiac unloading are related to 12-month prognosis during hospitalization for acute decompensated heart failure: an observational prospective study

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Introduction: Acute decompensated heart failure (ADHF) is associated with a high mortality and rehospitalization rate. The aim of this study was to assess whether echocardiographic markers of systolic and diastolic function, and their changes under treatment during hospitalization for ADHF, would predict 12-months mortality.

Methods: Adult patients admitted to our emergency department for ADHF between June 2015 and January 2018 were included if a complete transthoracic echocardiography (TTE) could be obtained within 12 hours of admission. TTE was repeated upon discharge. Baseline clinical and echocardiographic characteristics were collected on admission and at discharge, and outcome at 12 months was obtained by telephone interview. All parameters are given as median [interquartile range].

Results: A total of 221 patients were identified but 45 excluded because of in-hospital death (n = 8), early transfer to another hospital (n = 31) or refusal to perform discharge TTE (n = 6), leaving 176 patients for final analysis. Age was 83 [74-87] years, 95 (54%) were men and 89 (51%) were in sinus rhythm. Baseline TTE was performed within 6.6h [4.1-11.9] of admission and median duration of hospital stay was 13 days [9-19]. Admission ejection fraction (EF) was 45% [37-54] (29% HFrEF, 37% HFmrEF, 34% HFpEF). Between admission and discharge, significant changes were observed for global longitudinal LV strain (-10.3 [-7.2--15.1] to -11.8% [-8.1--15.0], p = 0.017), mitral E velocity (100 [80-124] to 96 cm/s [74-117], p = 0.001), E/e' ratio (16 [12-20] to 15 [11-19], p = 0.003, RV basal diameter (41 [36-45] to 41mm [34-44], p = 0.007), tricuspid regurgitation gradient (41 [34-52] to 35 mmHg [28-44], p = 0.0001 and vena cava diameter (22 [19-26] to 19 mm [15-23]. Deaths occurred in 35 (20%) at 12 months follow-up. In our multivariable model, none of the changes in TTE parameters was predictive of mortality. Age, LVEF and TAPSE measured at discharge, but not LV or RV strain, were identified as independent predictors of 12-months mortality (see figures O61-1 and 2).

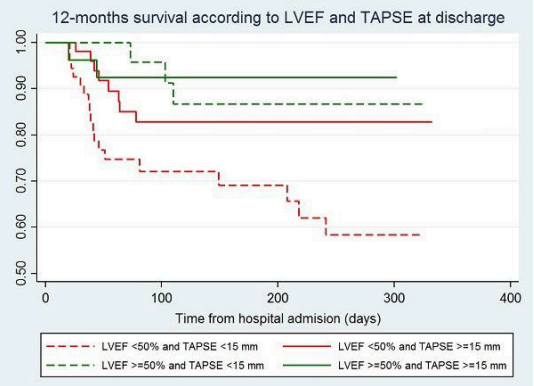
Conclusion: Several changes in TTE parameters were observed during hospitalization for ADHF, reflecting effective cardiac unloading with diuretic treatment. However, none of these changes appears to have prognostic significance. LVEF and TAPSE at discharge were identified as the only independent echocardiographic predictors of 12-months mortality, in addition to age.

Figure: O61-1. Multivariate analysis.

Independent echocardiographic predictors of 12-months mortality (discharge TTE)

	Multivariate logistic model			
	OR	95% CI	z	*p*
Age (years)	**1.09**	**1.02-1.18**	**2.51**	**0.01**
Male gender	2.00	0.69-5.81	1.27	0.20
LV ejection fraction (%)	**0.95**	**0.91-0.99**	**-2.41**	**0.02**
LV global longitudinal strain (|%|)	0.91	0.80-1.03	-1.49	0.14
RV basal diameter (mm)	1.07	0.99-1.16	1.81	0.07
TAPSE (mm)	**0.86**	**0.76-0.97**	**-2.50**	**0.01**

Figure: O61-2. Survival after admission for ADHF.



O62

Cardiac myosin-binding protein C for the diagnosis and long-term prognosis of acute heart failure

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Introduction: Cardiac myosin-binding protein C (cMyC) is a novel biomarker quantifying cardiac injury. Its utility for the diagnosis, prognosis, and therapy guidance in acute heart failure (AHF) is unclear.

Methods: In a prospective diagnostic multicentre study, unselected patients presenting with acute dyspnoea to the emergency department were enrolled. cMyC, high-sensitive cardiac troponin T (hs-cTnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma concentrations were measured. Two independent cardiologists/internists centrally adjudicated the final diagnosis using all individual patient´s information. Co-primary outcome measures were cMyC's: diagnostic safety and efficacy; prognostic accuracy.

Results: Among 1,330 recruited patients, 247 from an AHF substudy were not included in the diagnostic analy-

Figure: O62-1.

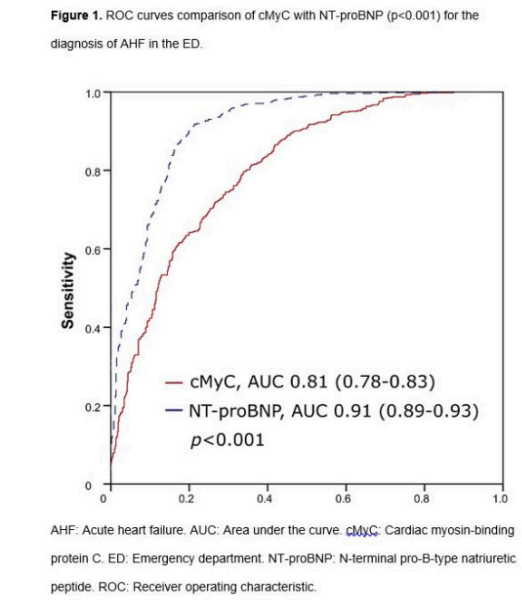
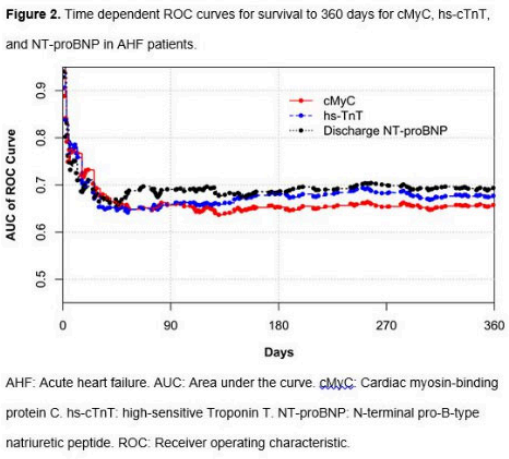


Figure: O62-2.



sis. Accordingly, 548 patients (51%) in this analysis had an adjudicated diagnosis of AHF. For the rapid rule-out of AHF, the cMyC cut-off concentration at 16 ng/L achieved a sensitivity of 95% (95% CI, 93-97%), a negative predictive value of 88% (95% CI, 84-92%), and allowed to rule-out 21% of the patients. Correspondingly, cMyC's efficacy and safety in the triage of AHF were slightly lower than NT-proBNP's. Of the 790 AHF patients in the prognostic analysis, 222 (28%) died during the 360 days' follow-up. Patients with cMyC plasma concentrations above the median had significantly shorter mean time to death (274 versus 320 days, $p = 0.001$). Compared to hs-cTnT and discharge NT-proBNP, cMyC showed non-inferior prognostic accuracy. No significant interactions between cMyC and cardiac medical therapies at discharge in predicting 360 days survival were present.

Conclusion: cMyC performs well in the rapid triage and prognosis of AHF.

O63

Tissue doppler imaging and outcomes in arrhythmogenic right ventricular cardiomyopathy

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Introduction: Echocardiography plays an important role in the diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). It is not known whether tissue Doppler imaging (TDI) is useful for predicting outcome in ARVC. In this study, we aimed at understanding the association of different functional echocardiographic parameters and TDI in particular with outcome in ARVC.

Methods: We studied 65 ARVC patients: 40 patients (62%) with definite, 8 (12%) with borderline, and 17 (26%) with possible ARVC according to the 2010 Task Force Criteria. Clinical and echocardiographic parameters including TDI were collected over a median follow-up time of 1420 days. The composite endpoints examined are described in the table.

Results: The major events endpoint was significantly associated with right ventricular (RV) structure and function such as RV EDA (β = 1.09, p<0.001), RA diameters (β = 2.02, p = 0.003), TAPSE (β = 0.85, p = 0.01), and tricuspid regurgitation (TR) (β = 7.61 p = 0.003). Furthermore, major events were associated with RV and left ventricular (LV) TDI-derived parameters such as tricuspid S', E', and A' (β = 0.72, p = 0.009, β = 0.78, p = 0.03, β = 0.77, p = 0.01), septal S' and E' (β = 0.61, p <0.001, β = 0.68, p = 0.01), and mitral S' and A' (β = 0.80, p = 0.04, β = 0.66, p = 0.01). In contrast to TDI, RV strain did not exhibit any association with major events.

Similarly, the complications endpoint was significantly associated with RV structure and function such as RV EDA (β = 1.11, p<0.001), RA diameters (β = 3.73, p<0.001), TAPSE (β = 0.84, p = 0.01), and tricuspid regurgitation (β = 4.13, p = 0.04). LV ejection fraction was significant as well (β = 0.93, p = 0.003). Furthermore, complications were associated with RV and LV TDI-derived parameters such as tricuspid S' and E' (β = 0.69, p = 0.002, β = 0.74, p = 0.008), septal S' and E' (β = 0.68, p = 0.04, β = 0.71, p = 0.04), and mitral S', E' and A' (β = 0.66, p<0.001, β = 0.63, p = 0.006, β = 0.70, p = 0.049). Several RV strain derived parameters were associated with complications: endocardial global longitudinal strain (β = 1.22, p = 0.03), peak strain of RV free wall basal segment (β = 8.98, p = 0.02), and peak strain of the septal basal segment (β = 156.30, p = 0.001).

Conclusions: TDI derived parameters were significantly associated with major events and complications in ARVC patients. Conventional echocardiographic parameters were predictive as well. In contrast, RV strain was only associated with complications. Hence, TDI is useful for follow-up and event prediction in ARVC.

Table: O63-1. Definitions, and events numbers of the study endpoints.

Endpoint	Events	Total Number (N, %)
'Major events' composite endpoint	Cardiovascular mortality, heart transplantation, resuscitation, and ventricular arrhythmia.	12 (18%)
'Complications´ composite endpoint	Thromboembolic events, cerebrovascular accidents, hospitalizations for heart failure, and arrhythmic syncopes.	11 (17%)