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UNIVERSITY OF BIRMINGHAM

BCTU

Birmingham Clinical Trials Unit

Spironolactone in atrial fibrillation with preserved cardiac contractility:

IMPRESS-AF Trial

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ESC Congress Paris 2019

Together with World Congress of Cardiology

Liverpool Centre for Cardiovascular Science

Declaration of interest

- I have nothing to declare

Introduction

In permanent AF

- poor outcomes and QoL despite stroke prevention and preserved EF
- prognosis worsens even on optimal rate control
- likely due to disturbed diastolic function, myocardial fibrosis/stiffening

Aldosterone

- increases cardiac collagen deposition/fibrosis
- expression of its cardiac receptors is increased in AF
- beneficial effects of spironolactone in recent onset AF in RACE-3 study

IMPRESS-AF

- Randomised, double-blinded, placebo-controlled trial
- ‘Permanent’ AF with preserved EF
- Spironolactone 25 mg od vs. Placebo (n=250) for 2 years

Objectives:

- To establish whether treatment with an aldosterone antagonist, spironolactone improves exercise tolerance, quality of life and diastolic function in permanent AF with preserved EF

Design

- Multicentre enrolment (family practices, hospital clinics)
- Single-site clinical management (City Hospital, Birmingham, UK)
- 1:1 Block randomisation
- Sponsor: University of Birmingham
- Managed by Birmingham Clinical Trial Units
- Funding: National Institute for Health Research (NIHR), UK
- EudraCT number 2014-003702-33
- clinicaltrial.gov (NCT02673463)

Outcomes

All assessed at 2 years

- **Primary end-points:**
  - Exercise tolerance (Peak VO_2)
- **Secondary end-points:**
  - 6-minute walking distance
  - Quality of life using MLWHF and EQ-5D questionnaires
  - Diastolic function assessed by E/E' ratio on echocardiography
  - All-cause hospital admissions
  - Spontaneous return to sinus rhythm on ECG

Population

- Age ≥50 years
- ‘Permanent’ AF
  - ≥1 year of AF on all prescreening encounters
  - Previously accepted rate control strategy
  - AF on ECG on the trial screening
- EF ≥55% on echocardiogram
- Controlled blood pressure

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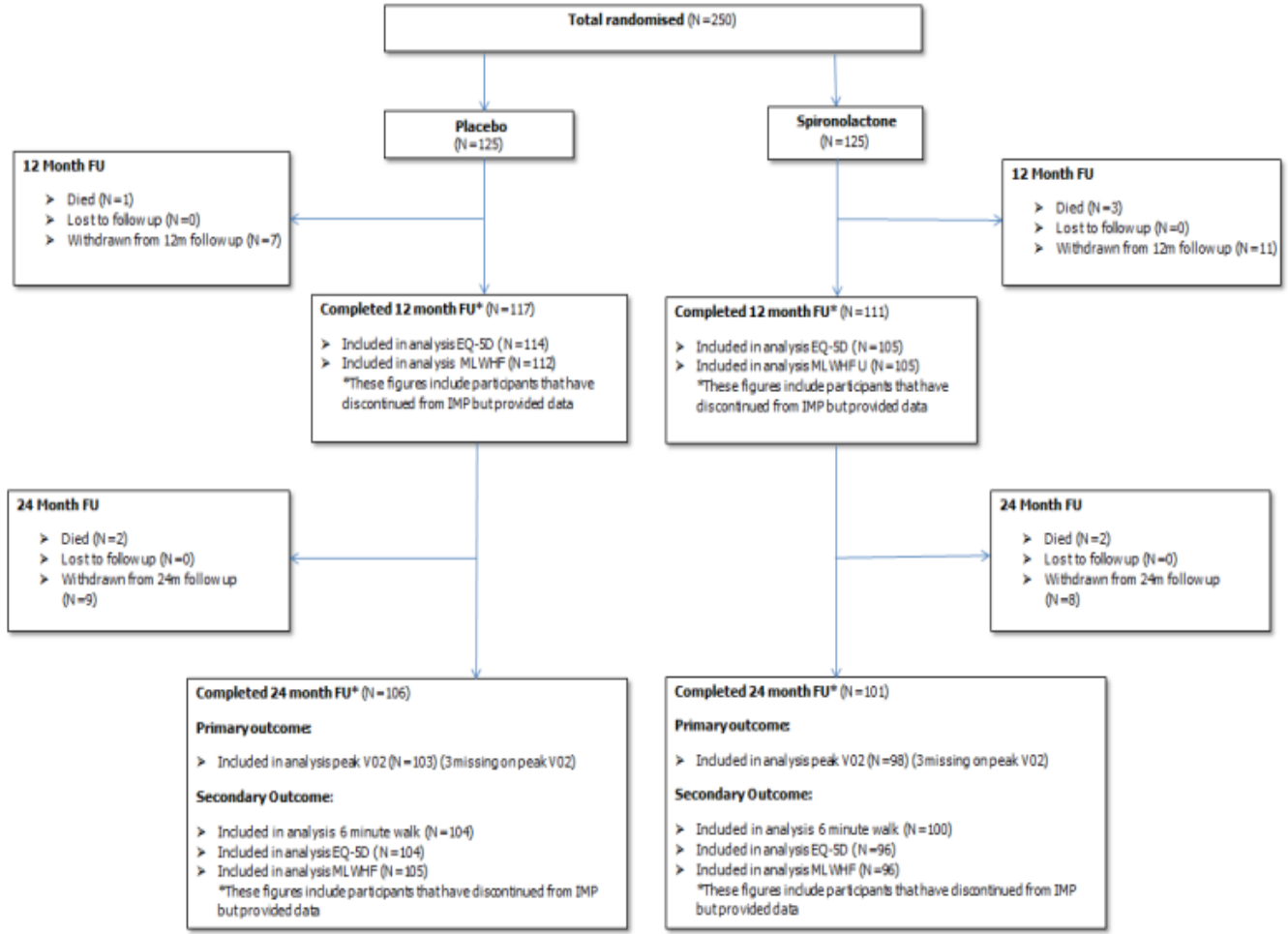
	Sp.	Pl.
Randomised	125	125
Died	5	3
Lost	0	0
Withdrawn	19	16
Completed	101	106



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Demographics

	Spironolactone	Placebo
Age, years	73 (68-77)	72 (67-78)
Female	28 (22%)	31 (25%)
White ethnicity	118 (94%)	118 (94%)
BMI, kg/m²	29 (26-33)	30 (26-34)
SBP/DBP, mmHg	130/75	129/74
Heart rate, /min	85 (74-99)	83 (74-97)

	Spironolactone	Placebo
EF, %	58 (57-62)	58 (56-63)
BNP, pg/mL	122 (73-230)	136 (82-241)
E/E' 10-14	41 (33%)	39 (31%)
E/E' ≥14	18 (14%)	22 (18%)
Diabetes	24 (19%)	21 (17%)
NOAC	60 (48%)	57 (46%)

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Primary Outcome

Peak VO_2	Spironolactone		Placebo		Treatment effect	p
	Mean (SD)	*n*	*Mean (SD)*	*n*	*Mean (95% CI)*	
Intention to treat analysis	14.0 (5.4)	103	14.5 (5.1)	106	-0.3 (-1.3 to 0.7)	0.58
Per protocol analysis	14.8 (4.3)	57	14.9 (4.9)	77	0.2 (-0.8 to 1.2)	0.67

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Primary Outcome: *subgroup analysis*

		Treatment effect	Estimate of difference (95% CI)	p
Peak VO_2	≤16 >16	-0.6 (-1.9 to 0.7) 0.1 (-1.5 to 1.6)	0.6 (-1.4 to 2.7)	0.54
Age (median)	≤73 >73	-1.4 (-2.8 to -0.1) 0.8 (-0.6 to 2.2)	2.2 (0.3 to 4.2)	0.03
Gender	Female Male	-0.4 (-2.5 to 1.7) -0.3 (-1.4 to 0.9)	0.1 (-2.3 to 2.6)	0.91

Primary Outcome: *subgroup analysis*

		Treatment effect	Estimate of difference (95% CI)	p
Systolic BP (median)	≤129 >129	-0.7 (-2.1 to 0.7) 0.2 (-1.2 to 1.6)	0.9 (-1.1 to 2.9)	0.36
Diastolic BP (median)	≤74 >74	-0.2 (-1.6 to 1.1) -0.3 (-1.8 to 1.1)	-0.1 (-2.1 to 1.9)	0.93
E/E’	<10 10-14 ≥14	-0.3 (-1.6 to 1.1) 0.1 (-1.8 to 1.9) -1.2 (-3.9 to 1.4)	-- 0.3 (-2.0 to 2.6) -1.0 (-3.9 to 2.0)	0.73

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Secondary Outcomes

Peak VO_2	Spironolactone		Placebo		Treatment effect *(95% CI)*	p
	Mean (SD)	*n*	*Mean (SD)*	*n*		
6MWT, m	313 (108)	105	330 (112)	107	-9 (-32 to 15)	0.48
E/E′ ratio	9.0 (3.1)	101	9.7 (3.6)	106	-0.7 (-1.5 to 0.2)	0.12
BNP, pg/mL	179 (171)	101	186 (110)	105	5 (-28 to 38)	0.77
EQ-5D-5L score	0.81 (0.26)	98	0.84 (0.21)	104	-0.01 (-0.06 to 0.04)	0.74
MLWHF score	17 (23)	96	15 (20)	104	0.5 (-4.3 to 5.3)	0.84

Secondary Outcomes

Restoration of sinus rhythm

Spironolactone	Placebo	Treatment effect	p
8 (8%)	4 (4%)	2.19 (0.64 to 7.52)	0.21

Hospitalisation for all causes: Participants with at least one event, n (

Spironolactone	Placebo	Treatment effect	p
18 (15%)	28 (23%)	0.65 (0.36 to 1.17)	0.15

Changes in Renal Function

	Spironolactone	Placebo	Mean difference (95% CI)	p
	Mean (SD)	Mean (SD)		
Creatinine	8.9 (13.8)	2.0 (12.1)	6.9 (3.4 to 10.5)	0.0002
eGFR	-6.8 (11.3)	-0.8 (12.3)	-6.0 (-9.3 to -2.8)	0.0003

Conclusions

- Treatment with spironolactone in permanent AF with preserved EF:

  - does not improve exercise tolerance, QoL and diastolic function

  - leads to worsening of renal function

- A larger study would be unlikely to change the conclusions of the IMPRESS-AF trial

Acknowledgments:

National Institute for Health Research
Trial Steering Committee (Chair Prof Diana A Gorog); DMEC (Chair Dr Derick Todd)

Applicants	Patient Recruitment and Management	Birmingham Clinical Trial Unit
•Prof Gregory YH Lip (PI) •Prof Paulus Kirchhof (co-PI) •Dr Eduard Shantsila (co-PI) •Prof Paramjit S Gill •Prof Melanie Calvert •Prof James P Fisher •Mr Roger L Holder	•Trial Research Fellows •Dr Farhan Shahid •Dr Christos Voukalis •Dr Marco Proietti •Sr Ronnie Haynes •Sr Rebecca Brown	•Prof Jonathan Deeks •Dr Yongzhong Sun •Gurdip Heer •Alexandra Enocson •Margaret Grant •Sarah Tearne •Kate Flatcher •Hollie Caulfield