Inhibition of the renin-angiotensin system protects lung function in type 2 diabetes: The Fremantle Diabetes Study Phase II

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Background

- The pulmonary capillary endothelium is a site at which angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II
- Since angiotensin II has pro-inflammatory and pro-fibrotic properties, we postulated that ACE inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) attenuate progressive restrictive lung disease complicating type 2 diabetes

Aim

- To assess the relationship between changes in lung function and ACE-I or ARB exposure in adults with type 2 diabetes aged 25-94 years recruited to the community-based Fremantle Diabetes Study Phase II (FDS2) between 2008-2011 and followed biennially for up to 6 years

Patients and Methods

- At baseline and each biennial review, participants underwent comprehensive physical, biochemical and questionnaire assessments, including spirometry (EasyOne™ digital spirometer)
- On average, three spirometry recordings were available per person at each assessment. The highest FEV1 and FVC results were used¹
- Predicted values were estimated using the Quanjer GLI-2012 reference equations (restricted to people under 95 years old)²

Results

- Of 1551 participants with type 2 diabetes, 1406 (90.7%) performed acceptable lung function tests and were <95 years of age at baseline - their characteristics and those of the 145 who did not attempt or did not perform an acceptable test or were ≥95 years of age are summarised in Table 1
- At baseline, for the 1406 participants, mean ± SD FEV1 and FVC percentage predicted (%pred) and predicted FEV1/FVC were 82.7 ± 19.1%, 85.9 ± 17.9%, and 0.78 ± 0.02, respectively

Table 1: Baseline characteristics of participants by ability to perform acceptable spirometry and aged <95 years

	Acceptable and <95 years of age	Unacceptable or ≥95 years of age	P-value
Number (%)	1406 (90.7)	145 (9.3)	
Age (years)	65.4 ± 11.2	68.4 ± 14.9	0.020
Female (%)	46.8	60.7	0.002
Current smoker (%)	9.9	17.1	0.013
Diabetes duration (years)	8.0 [2.5-15.5]	12.0 [4.5-20.1]	<0.001
HbA _{1c} (%)	6.8 [6.2-7.7]	7.1 [6.3-8.5]	0.037
HbA _{1c} (mmol/mol)	51 [44-61]	54 [45-69]	0.037
ACE-I or ARB use (%)	65.0	63.4	0.72
On asthma medications (%)	9.1	10.0	0.75
Current respiratory illness (%)	17.7	22.8	0.14

- 1022 (65.9%) participants were followed up, had adequate spirometry, complete medication data, and time between relevant consecutive assessments was ≥1.0 and <3.0 years
- 46 were counted twice due to starting then stopping an ACE-I/ARB or vice versa
- During 4.3 ± 2.7 years of follow-up, 173 and 129 participants, respectively, with valid lung function data 1.0-2.9 years apart, self-reported starting or stopping an ACE-I/ARB, whilst 214 never and 552 always took an ACE-I/ARB
- The mean (95% CI) change in FEV1 %pred, FVC %pred and FEV1/FVC predicted either side of the treatment change or, in the case of stable or no treatment with ACE-I/ARB, the first two consecutive biennial assessments are shown in Table 2
- Mean FVC %pred decreased significantly by 3.6% in participants stopping ACE-I/ARB treatment
- FEV1/FVC predicted reduced significantly and consistently by 0.003 for all treatment groups between biennial assessments

Conclusion

- These data suggest that the protection against restrictive lung damage afforded by ACE-I/ARB in type 2 diabetes may be lost when these drugs are withdrawn

References: 1. National Asthma Council Australia. Asthma and Lung Function Tests. Melbourne, National Asthma Council Australia, 2012);
2. <http://www.lungfunction.org/tools.html>

Table 2: Mean change (Δ) over time (95% confidence intervals) in lung function in patients with type 2 diabetes by ACE-I or ARB use (initiation during follow-up (started); cessation during follow-up (stopped); no use (none); chronic use (stable))

ACE-I or ARB use	N	Time between assessments (years)	Mean ΔFEV1 % predicted (95% CI)	Mean ΔFVC % predicted (95% CI)	Mean ΔFEV1/FVC predicted (95% CI)
None	214	2.0 ± 0.2	1.46 (-0.19 to 3.03)	-0.23 (-1.53 to 1.07)	-0.0026 (-0.0028 to -0.0024)
Stable	552	2.1 ± 0.2	0.46 (-0.47 to 1.39)	-1.05 (-2.11 to 0.01)	-0.0026 (-0.0027 to -0.0025)
Started	173	2.1 ± 0.2	-0.29 (-2.15 to 1.58)	-1.18 (-2.99 to 0.63)	-0.0027 (-0.0029 to -0.0026)
Stopped	129	2.2 ± 0.2	-1.65 (-4.00 to 0.71)	-3.64 (-6.10 to -1.17)	-0.0025 (-0.0027 to -0.0023)