Keywords: Parkinson's disease; Rotigotine; Non-ergot dopamine agonists; Adverse drug reactions; Valvular heart disease; Valvular regurgitation; Fibrotic reactions; Echocardiography

Introduction

Treatment of Parkinson's disease (PD) is still a challenge and focuses on the symptomatic control of motor and non-motor symptoms without

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changes cause sti ening and retraction of valves leading to insu cient lea et coaptation and clinically signi cant regurgitation that required surgical valve replacement in some patients.

Several echocardiographic prevalence studies reported increased risk of valvular heart disease (VHD) in patients taking ergot DAs (cabergoline, pergolide) compared to non-ergot DAs (pramipexole, ropinirole) [7-9] and an association between cumulative dose and severity of valve regurgitation [9]. A systematic review con rmed these ndings assessing an increased risk of cardiac valve regurgitation associated with the use of ergot DAs and not of non-ergot DAs [10]. However, published studies of pergolide did not reveal valvulopathy in about two-thirds of patients despite several years of exposure [11]. erefore, the role of individual vulnerability and susceptibility as well as the reversibility of brotic reactions still have to be clari ed [12,13].

e non-ergot DA rotigotine has been developed as an e ective antiparkinsonian drug acting as a full agonist on D3, D2 and D1 dopamine receptors through a novel transdermal delivery system [14]. It exerts low a nity to -adrenergic receptors and no relevant a nity to the 5-HT2B receptor. A recent study assessed the impact of rotigotine on cardiovascular autonomic function in 20 de novo PD patients [15]. Rotigotine did not modify cardiovascular parameters, including orthostatic blood pressure response and cardiac responses to the valsalva maneuver or to deep breathing.

Rotigotine was approved and admitted to the European market in 2006. Systematic data on the long term safety associated with the cumulative dose of the compound a er several years of exposure were missing. On request by the EMA (European Medicines Agency) we initiated in 2011 the rst prospective trial to assess the possible risk of VHD in PD patients receiving rotigotine compared to other non-ergot DA agonists over a 2-year period.

Patients and Methods

From March 2011 (rst patient in) to April 2014 (last patient out), we conducted a prospective, multicenter, open-label, 2-year echocardiographic study in PD patients taking rotigotine or other non-ergot DA (piribedil, pramipexole, ropinirole). e study protocol was approved by the ethics committee of the Philipps University of Marburg in agreement with the ethical principles of the Declaration of Helsinki. Patients were recruited from an outpatient setting at 11 centres of o ce-based neurologists in Germany. All patients' gave their written informed consent to participate.

Eligible patients were Caucasian men and women aged > 18 years with a diagnosis of PD (UK PD Society Brain Bank Clinical

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