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Nutrition, Metabolism & Cardiovascular Diseases

SPECIAL ARTICLE

Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: Impact on cardiovascular events. A randomized controlled trial

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KEYWORDS
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Abstract *Background and aims:* Metformin is the first-line therapy in type 2 diabetes. In patients inadequately controlled with metformin, the addition of a sulfonylurea or pioglitazone are equally plausible options to improve glycemic control. However, these drugs have profound differences in their mechanism of action, side effects, and impact on cardiovascular risk factors. A formal comparison of these two therapies in terms of cardiovascular morbidity and mortality is lacking. The TOSCA.IT study was designed to explore the effects of adding pioglitazone or a sulfonylurea on cardiovascular events in type 2 diabetic patients inadequately controlled with metformin.

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Methods: Multicentre, randomized, open label, parallel group trial of 48 month duration. Type 2 diabetic subjects, 50—75 years, BMI 20—45 Kg/m^2, on secondary failure to metformin monotherapy will be randomized to add-on a sulfonylurea or pioglitazone. The primary efficacy outcome is a composite endpoint of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, and unplanned coronary revascularization. Principal secondary outcome is a composite ischemic endpoint of sudden death, fatal and non-fatal myocardial infarction and stroke, endovascular or surgical intervention on the coronary, leg or carotid arteries, major amputations. Side effects, quality of life and economic costs will also be evaluated. Efficacy, safety, tolerability, and study conduct will be monitored by an independent Data Safety Monitoring Board. End points will be adjudicated by an independent external committee.
Conclusions: TOSCA.IT is the first on-going study investigating the head-to-head comparison of adding a sulfonylurea or pioglitazone to existing metformin treatment in terms of hard cardiovascular outcomes.
Registration: Clinicaltrials.gov ID NCT00700856.

Introduction

There is general agreement that metformin, if not contraindicated and well tolerated, should be the first agent in the treatment of type 2 diabetes [1—5], but considerable uncertainty does exists on the best therapeutic option as second line treatment after metformin failure. According to recent guidelines, in patients inadequately controlled with metformin, the addition of a sulfonylurea (SU) or pioglitazone are equally plausible options to improve glycemic control [6,7]. However, these two drugs have profound differences in their mechanisms of action, side effects, and impact on cardiovascular (CV) risk factors.

SUs have been available for a long time and are the least expensive and more widely used oral hypoglycemic agents. They stimulate insulin secretion by binding the ATP-sensitive potassium channels in the beta cells. SUs rapidly lower blood glucose, but are associated with modest weight gain, increased risk of hypoglycaemia and a secondary failure rate that exceeds other drugs [8]. In addition, the CV effects of SUs are debated. These agents bind to various degrees the ATP channels in the cardiomyocytes thus blunting the myocardial preconditioning mechanism [9,10]. To what extent this may impact CV morbidity and mortality is unclear. Observational studies report higher all-cause and CV mortality with SUs vs. metformin monotherapy [11—16] and in case series of coronary angioplasty, patients on SUs had higher in-hospital mortality than patients on other treatments [17]. To the contrary, data from the French registry on Acute ST and non ST-elevation Myocardial Infarction (FAST-MI) have shown a better outcome in patients on SUs at admission as compared with patients on other treatments [18]. As for intervention studies, in the University Group Diabetes Program (UGDP) [19] patients receiving tolbutamide experienced more CV events than those treated with insulin, whereas in the UKPDS there is no evidence of an adverse effect of SUs on CVD outcomes [20] and more recently, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) study, intensive therapy with gliclazide significantly reduced the risk of microvascular endpoint, with no detrimental effects on macrovascular events [21]. The thiazolidinediones (TZDs) are insulin sensitizing agents [22]: they lower blood glucose without causing hypoglycaemia and provide more durable glycemic effect than other drugs [8]. Pioglitazone also improves lipid profile, blood pressure, albuminuria, and inflammatory and procoagulant markers, an array of effects which may translate into better CV outcomes. Furthermore the PROACTIVE (PROspective pioglitAzone Clinical Trial In macroVascular Events) study has shown that the addition of pioglitazone to the hypoglycaemic therapy in patients with type 2 diabetes and overt macrovascular disease significantly reduced a composite end point of all-cause mortality, nonfatal MI and stroke as compared to placebo [23]. In addition the CHICAGO and PERISCOPE studies have shown that pioglitazone, as compared with glimepiride, reduces the progression of carotid intima—media thickness [24] and the progression of intracoronary atherosclerosis [25]. Recognized side effects of pioglitazone, which may restrain a more common use, include unwanted weight gain, fluid retention leading to edema and/or heart failure in predisposed individuals, increased risk of bone fractures and possibly bladder cancer [26,27].

Due to the paucity of experimental evidence, the algorithms for managing glycemia recommended by the several professional associations and scientific societies are largely based on the opinion of experts and are not fully concordant [1—7]. In particular, the CVD effects of glucose-lowering agents remain debated. The Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents. Intervention Trial (TOSCA.IT) study was designed and initiated to compare the effects of the addition of SUs vs. pioglitazone on CV events in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Durability of glucose control, side effects, quality of life and costs will also be evaluated.

Methods

Research design

The study (protocol number FARM6T9CET), registered in the clinicaltrials.gov with ID NCT00700856, is a multicentre,

parallel-group trial of 48 months duration. A Prospective Randomized Open Blinded End-Point Evaluation (PROBE) design is employed. The protocol has been approved by the Ethics Review Committee/Insitutional Review Board of the Coordinating Centre and of each participating centre. The study is carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent must be obtained from participants before beginning any protocol-specific procedure and the participants are informed of their right to withdraw from the study at any time. Standard procedures for assuring full respect of privacy are undertaken. The conduct of each participating center is monitored by regular visits of professional monitors.

Efficacy end points

The primary efficacy outcome is a composite of all-cause mortality, nonfatal myocardial infarction (MI) (including silent MI), nonfatal stroke, unplanned coronary revascularization. The principal secondary outcome is a composite ischemic end point of sudden death, fatal and non-fatal MI (including silent MI), fatal and nonfatal stroke, major leg amputation (above the ankle), endovascular or surgical interventions on the coronary, leg or carotid arteries.

Other secondary outcomes are:

1) A composite CV endpoint including the primary endpoint plus hospitalization for heart failure, endovascular or surgical intervention on the coronary, leg or carotid arteries, incident angina or intermittent claudication;
2) All cases of heart failure;
3) A microvascular composite endpoint including: incident macroalbuminuria, or doubling of baseline plasma creatinine, or a creatinine clearance reduction of 20 ml/min/1.73 m^2 or plasma creatinine $>$3.3 mg/dl, or dialysis;
4) Glucose control (changes from baseline in HbA1c, time to failure of oral hypoglycaemic therapy, defined as HbA1c $>$8.0% on two occasions three months apart);
5) Changes from baseline of the CV risk factors profile (lipids, blood pressure, microalbuminuria, inflammation markers, waist circumference).

A Clinical Endpoints Committee (CEC) of expert clinicians (cardiologists, diabetologists, internal medicine specialists and epidemiologists), blind to study medication assignment, is reviewing and adjudicating the outcomes included in the primary endpoint plus all the cases of heart failure and revascularization according to predefined criteria.

Visits and procedures

The eligibility criteria are listed in Table 1. Eligible patients are randomized to one of two treatments (Fig. 1): metformin + sulfonylurea (glibenclamide 5 mg or gliclazide 30 mg or glimepiride 2 mg used according to local practice) or metformin + pioglitazone (15 mg). Treatment is centrally assigned by telephone after verification of eligibility. The treatment allocation schedule is computer generated in blocks and stratified according to centre and previous CV events. The investigators are masked to the randomization sequences.

An outline of the study procedures is given in Table 2. At screening the study aims and procedures are extensively discussed with the patients, a written informed consent is obtained and the inclusion/exclusion criteria are assessed. Patients deemed eligible and willing to participate are enrolled. At baseline (randomization visit) the inclusion/exclusion criteria are reassessed, a complete medical history, including prior CV events and use of medications, is recorded; a complete physical examination, including standardised measurements of blood pressure, body weight, height, waist and hip circumference and a standard

Table 1 Overview of inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
- Type 2 diabetes of at least 2 years duration	- Type 1 diabetes
- Males and females, age 50–75 years	- Previous treatment with TDZs within the last six months
- BMI 20–45 Kg/m^2	- Contraindication/intolerance to metformin or SUs or TZDs
- Stable treatment for the last two months with metformin in monotherapy at 2 g/day	- Documented coronary or cerebrovascular events within the previous 3 months
- HbA1c $\geq$ 7.0% and $\leq$9.0%	- Serum creatinine $>$ 1.5 mg/dl
	- History of congestive heart failure, NYHA class I or higher
	- Chronic use of glucocorticoids
	- Ischemic ulcer or gangrene of lower extremities
	- Liver cirrhosis or severe hepatic dysfunction (ALT $>$ 2.5 times the upper normal limit)
	- Pregnancy or breast feeding
	- Cancer, substance abuse, or any health problem that may interfere with the compliance to the study protocol or limit life expectancy

BMI: body mass index; HbA1c: glycated hemoglobin; SUs: sulfonylureas; TZDs: thiazolidinediones; NYHA: New York Heart Association; ALT: Alanine aminotransferase.

Table 2 Overview of the study assessments.

Visit	Screening	Baseline	Year 1				Years 2–4	
			1 mo	3 mo	6 mo	12 mo	Semiannually	Annually
Inclusion/exclusion criteria assessment	x	x						
Informed consent obtainment	x							
Clinical history	x	x	x	x	x	x	x	x
Anthropometry	x	x	x	x	x	x	x	x
Clinical examination	x	x	x	x	x	x	x	x
ECG		x				x		x
Food frequency questionnaire		x				x		x
Quality of life questionnaire		x			x			x
Economic questionnaire		x			x			x
Biochemistry								
HbA1c		x			x	x	x	x
Lipids		x				x		x
Creatinine		x				x		x
Microalbuminuria		x				x		x
PCR		x				x		x
Urinalysis and assessment of hematuria[a]		x			x	x	x	x
Hypoglycaemia		x	x	x	x	x	x	x
Compliance		x	x	x	x	x	x	x
Endpoint events		x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x

Plasma lipids include: total cholesterol, HDL cholesterol and triglycerides.
[a] Starting from January 2012.

12-lead ECG, is performed. Fasting blood samples and a morning spot urine sample are collected for biochemical analyses (see Table 2). Dietary habits are assessed using a validated food frequency questionnaire — the Italian version of the European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire. Quality of life and economic costs will also be assessed with the use of standard questionnaires. All participants are instructed to perform home glucose monitoring (one full day glucose profile per week) and to record the number and severity of hypoglycaemic events.

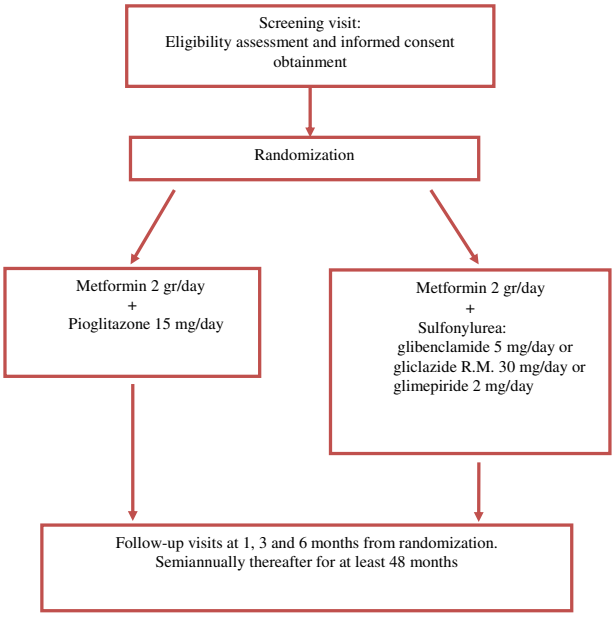

Figure 1 Flow chart of the study design.

Follow-up is scheduled at 1, 3, and 6 months after randomization and biannually thereafter (Table 2). At each visit adherence to the study protocol is assessed, information on the occurrence of any adverse or endpoint event(s) is collected. Anthropometry, blood pressure and heart rate are measured. Since January 2012, due to regulatory concerns regarding pioglitazone and the risk of bladder cancer, macroscopic hematuria is also assessed at each visit. HbA1c is measured semiannually. A standard 12-lead ECG, fasting plasma lipids (total cholesterol, HDL cholesterol, triglycerides), creatinine, high sensitivity C-reactive protein (hsCRP), and urinary excretion of albumin and creatinine are performed annually. The patient's home glucose readings and the records of hypoglycaemia are reviewed at each visit. The metformin dose remains constant (2 g/day) throughout the study. The add-on drugs will be up-titrated at any follow-up visit, if necessary, based on home glucose monitoring (i.e fasting glucose >120 mg/dl or post prandial glucose >160 mg/dl in more than 50% of the home glucose readings performed over the last 8 weeks period). The maximum daily dose is 15 mg for glibenclamide, 120 mg for gliclazide, 6 mg for glimepiride, and 45 mg for pioglitazone. If, despite the maximal daily dose of the drugs has been reached, blood glucose control is still unsatisfactory, adherence to treatments is assessed, lifestyle recommendations are reinforced and HbA1c is re-

evaluated after three months. A confirmed HbA1c >8.0%, will lead to add on a bed-time injection of basal insulin (glargine) and prandial rapid acting insulin boluses, if glucose control is still unsatisfactory. Insulin titration is performed according to a pre-defined algorithm based on self-monitored fasting capillary glucose [28].

Concomitant medications are allowed throughout the study. Initiation and dose adjustments of antihypertensive, lipid-lowering and antiplatelet agents are made according to current guidelines [7] and clinical judgment. The trade name and dosage of all medications are recorded at each visit. Ad hoc developed electronic Case Report Forms (CRFs) are used for data collection, data is web-transmitted to the Data Monitoring Centre where the forms are checked for missing or incoherent data. An electronic data base is being created using a standardized procedure for data input.

Laboratory measurements

A fasting blood sample is obtained in the morning, immediately centrifuged and serum is aliquoted; a spot urine sample is also collected and aliquoted. The samples are transferred within two days, under appropriate conditions, to the central laboratory and processed on arrival. Extra samples are stored (−80 °C) for future analyses. Glycated hemoglobin is measured by HPLC (ion-exchange chromatography) using an automatic analyzer (Adams A_{1c} HA-8160, Menarini). Lipids, plasma and urine creatinine, and albuminuria are measured on the automatic analyzer MODULAR SWA (Roche Diagnostics, Italy) respectively by enzymatic-colorimetric methods, ECLIA and immunoturbidimetry. CRP is determined by a high sensitive immunonephelometric method (CardioPhase hs CRP, SIEMENS) on the BN™ II System (SIEMENS). Brain Natriuretic peptide (NT-proBNP) can be measured centrally at any time, according to the researchers judgment, in case signs or symptoms suggestive of heart failure develop. Any other test judged useful from the clinical stand point is performed at each centre.

Safety assessment

The study drugs are largely used for the treatment of diabetes, no additional risk, besides the known side effects of the drugs, is envisaged. The occurrence of adverse events (hypoglycaemic events, weight gain, peripheral edema, heart failure episodes, etc.) is strictly monitored. Hypoglycaemia is defined as a documented glucose value lower than 60 mg/dl and graded as moderate (not requiring help for treatment) or severe (requiring assistance for treatment or associated with loss of consciousness or requiring glucagon or endovenous glucose for treatment).

Patients will stop the study medications if any of the followings occurs: alanine amino transferase increases three times from baseline on two consecutive occasions, one month apart; heart failure, evaluated according to the American Heart Association and the American Diabetes Association consensus on glitazones and heart failure [29], or any other medical condition(s) that contraindicates the use of the study medication(s). In addition, in the pioglitazone arm, treatment will be withdrawn if macroscopic hematuria of unknown origin occurs at any time or bladder cancer is diagnosed. Patients who are withdrawn from the study medications enter a follow-up observational period following the scheduled protocol visits. An external Data Safety and Monitoring Board (DSMB) will monitor safety throughout the study and review the critical efficacy endpoints.

Pharmacoeconomic evaluation

The health status and pharmacoeconomic outcomes are assessed by a standard questionnaire (EQ 5D 5 levels). Direct and indirect costs of the two treatment regimens will be evaluated; the cost-effectiveness analysis (CEA), cost-consequence analysis (CCA) and cost-minimization analysis (CMA) will be conducted as appropriate.

Sample size estimation

The sample size is estimated to detect a reduction in the risk of events of 20% (HR = 0.80; metformin + pioglitazone vs. metformin + SU) with a statistical power of 80% and a $p < 0.05$, one tail. The estimated occurrence rate of the primary end point is 3.5% per annum [30—32] and the estimated loss to follow-up is 5%. The efficacy analysis will be event driven. Given these assumptions, a total of 3371 patients will be enrolled and a total of 498 events have to be reached to complete the study. The planned follow-up is 4 years; however results of recent trials have shown that the rate of occurrence of the primary end point may actually be lower than we anticipate, therefore a longer follow-up may be necessary to reach the needed number of events.

Statistical analysis

The trial is event driven and the efficacy analysis will be conducted according to intention to treat. Based on the number of occurring events, individual components of the primary and secondary composite endpoint will also be analysed.

Incidence rates will be evaluated using Kaplan—Meier survival curves that will be compared (metformin + pioglitazone vs. metformin + SU) using logrank analysis. Treatment efficacy will be assessed by multivariate analyses using Cox's regression.

Other secondary analyses will include the evaluation of efficacy of metformin + pioglitazone vs. metformin + SU on pre-defined secondary end-points. Side effects, direct and indirect costs will also be compared in the two study arms. Incidence and severity of hypoglycaemia will be compared between arms using a Poisson regression model. Subgroups analyses will be performed according to gender, BMI and prior cardiovascular events.

Organizational characteristics

The study is conducted at Diabetes Clinics by diabetes specialists (a complete list of the study participants is reported in Appendix). More than one hundred clinics distributed all over Italy are currently participating in the

study. Screening and follow-up visits are performed according to a standard protocol described in detail in the manual of operation (MOP). Prior to the initiation of the study, the investigators attended training and standardization sessions in order to minimize inter-observer variability.

The Coordinating Centre is based at the Department of Clinical and Experimental Medicine of the "Federico II" University of Naples, Italy, and is responsible for the preparation of the study protocol, the Manual of Operations (MOP) and the organization of the training sessions for the field investigators.

The Centre for the Data Monitoring and Randomization, based at the Consorzio Mario Negri Sud in Santa Maria Imbaro (CH), provides a centralized telephone randomization system for the patients allocation to study medications, and is responsible for data management and analyses.

The ECG reading will be performed at the Centro Studi ANMCO in Florence by certified readers blinded to treatment arm and according to a standard protocol.

The biochemical analyses are performed at the Department of Laboratory Medicine, Desio Hospital, Monza-Brianza, Italy.

The food frequency questionnaire is produced and electronically read at REGGIANI S.p.A., Varese, Italy; nutrients, food groups, glycemic index, glycemic load and oxidative capacity will be calculated at the Nutritional Epidemiology Unit of the Department of Preventive & Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, with the use of an ad hoc developed software.

The Pharmacoeconomic and Pharmacovigilance Units are based at the "Federico II" University of Naples, Italy.

Preliminary data

To date 2450 patients have been enrolled (i.e. 73% of the total sample required). End of recruitment is planned within June 2013. The general characteristics of the participants are given in Table 3. Overall they are middle aged, obese, with a mean diabetes duration of 8.6 ± 5.8 years, a mean HbA1c of 7.7 ± 0.5%. On average, lipids and blood pressure are well controlled; 56% are on lipid lowering drugs, 68% report taking antihypertensive medications, 42% use antiplatelet medications and 10.4% report a prior CV event.

Table 3 General characteristics of the study participants (n = 2450).

	$M \pm$ SD or n (%)
Age	62.8 ± 6.6
Males n (%)	1318 (57.4)
BMI (kg/m^2)	30.3 ± 4.4
Waist circumference (cm)	104.3 ± 11.1
Diabetes duration (years)	8.6 ± 5.8
HbA1c%	7.7 ± 0.5
Total cholesterol (mmol/l)	4.68 ± 0.95
HDL cholesterol (mmol/l)	1.20 ± 0.37
LDL cholesterol (mmol/l)	2.69 ± 0.82
Triglycerides (mmol/l)	1.74 ± 0.94
Systolic blood pressure (mmHg)	134.2 ± 14.9
Diastolic blood pressure (mmHg)	79.7 ± 8.5
Microalbuminuria	467 (20)
Antihypertensive treatment	1567 (68)
Antiplatelet treatment	953 (42)
Hypolipidemic treatment	1280 (56)
Prior CV event(s)	238 (10.4)

Discussion

In clinical practice, the beneficial effects of the various hypoglycaemic treatments must be considered not only in relation to their glucose lowering effects (reduction of HbA1c, time to failure of glucose control), but also in relation to their impact on the risk for the long term complications of diabetes. In addition the benefits have to be balanced against safety (drug-specific side effects, risk of hypoglycaemias, effects on body weight, etc.).

So far, no study has provided a direct (head to head) comparison of different anti-diabetic drugs on long term complications. As a consequence, the several compounds (SUs, pioglitazone, glinides, DPP-4 inhibitors, etc.) have been indicated by current guidelines and expert recommendations as equally plausible options when metformin monotherapy fails, despite the fact that mechanisms of action are different, durability is not superimposable, safety profile and costs are not identical [6,7].

Comparative effectiveness research, particularly with regard to CV outcomes, has a high priority in order to allow evidence based medical decisions, improve public health and optimize cost effectiveness in the management of type 2 diabetes.

The Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents. Intervention Trial (TOSCA.IT study) is the first trial designed as a head-to-head comparison of two hypoglycaemic strategies on CV endpoints and is also the only ongoing study that evaluates the potential benefits of TZDs on cardiovascular disease, as the TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation) has been terminated prematurely owing to concerns on the CV safety of rosiglitazone [33].

The TOSCA.IT study will also shed light on other relevant issues, such as glucose-lowering effects, time to failure of oral hypoglycaemic therapy, quality of life, side effects and economic costs, including the costs of adverse effects, particularly hypoglycaemia. This information is lacking and is strongly needed to allow an evidence based choice for the management of type 2 diabetes.

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Duality of interest

O Vaccaro, M Masulli, A Nicolucci, CB Giorda, P Mocarelli, S Squatrito, AA Rivellese and G Riccardi declare that they have no duality of interest associated with this manuscript.

E Bonora is a member of the Italian Takeda Advisory Board and has received a research grant from Takeda in the last 2 years. S Del Prato has served on advisory panels for Novartis Pharmaceuticals, Merck & Co., Roche Pharmaceuticals, Eli Lilly and Co., Boehringer Ingelheim, Novo Nordisk, Takeda Pharmaceuticals, Intarcia Therapeutics Inc., and Astra Zeneca and, as speaker from Novartis, Sanofi-aventis, Eli Lilly and Co. and Bristol-Myers Squibb. Research support was funded by Merck&Co., Novo Nordisk, Takeda Pharmaceuticals, Novartis Pharmaceuticals. AP Maggioni is a member of the Steering Committee of trials sponsored by Sanofi—Aventis and Eli Lilly.

Contribution statement

Vaccaro, M Masulli, E Bonora, S Del Prato, AA Rivellese, S Squatrito, G Riccardi were involved in the conception and design of the study protocol, drafting of the article and final approval of the version to be published. A Nicolucci was involved in the design of the study and was responsible for data analysis. CB Giorda, AP Maggioni, P Mocarelli revised the manuscript critically providing important intellectual content and final approval of the version to be published.

Appendix A

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