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Cardiovascular risk factors control according to diabetes status and prior cardiovascular events in patients managed in different settings

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ABSTRACT

Aims: To document in recent cohorts the degree of control of major cardiovascular (CV) risk factors according to diabetes status and prior CV disease in different settings.

Methods: We studied men and women aged 50–75 years of whom 3028 with type 2 diabetes mellitus (T2DM) managed at diabetes clinics participants of the TOSCA.IT (NCT00700856) study recruited in 2008–2014; 742 with T2DM managed mainly in primary care and 6753 without diabetes participating in the Moli-sani (NCT03242109) study and recruited in 2005–2010 from an adult general population.

Results: Among people without a prior CV event people with diabetes managed at diabetes clinics have lower LDL-cholesterol and blood pressure and a more frequent use of lipid-lowering and antihypertensive medications as compared to people with diabetes managed mainly in primary care and to people without diabetes. The proportions achieving the recommended treatment targets are respectively 47.4% vs 33.4% vs 29.5% for LDL-cholesterol and 42.6% vs 9.5% vs 47.4% for blood pressure. Figures for the participants with prior CV events were 26.8% vs 15.1% vs 42.5% for LDL-cholesterol and 43.8% vs 8.5% vs 43.6% for blood pressure.

Conclusions: The study documents that in modern cohorts a large proportion of people with or without diabetes does not achieve the treatment targets for LDL-cholesterol and blood pressure, both in primary and secondary CV prevention. People with diabetes attending diabetes clinics achieve a better control of major CV risk factors than those managed mainly in primary care, thus highlighting the relevant role of a structured model of care.

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1. Introduction

Cardiovascular disease (CVD) represents the major cause of hospital admission in middle-aged and older people and remains among the leading causes of death worldwide with large geographic differences [1,2]. The burden of CVD in the population with diabetes mellitus is significantly higher than in other populations and is largely maintained by the high prevalence of modifiable cardiovascular risk factors [3–5]. The optimal correction of these risk factors has proved to be highly effective in reducing CV morbidity and mortality in people with or without diabetes [6–8]. To this aim treatment targets for the management of major CV risk factors in primary and secondary cardiovascular prevention are described in several guidelines [9,10], but their implementation in clinical practice has been repeatedly reported as suboptimal in that the control of major cardiovascular risk factors is unsatisfactory and the use of medication with proven CV benefits, such as statins and antihypertensive medications, is insufficient [11–13]. In addition, there is evidence that the quality of care differs across the population with diabetes and this can bear on prognosis [14–16]. The available audits of cardiovascular risk management in clinical practice are based on cohorts established decades ago and mainly concern patients at high risk, whereas little is known about CV risk factors control in more recent cohorts at lower absolute cardiovascular risk, more representative of the reality of clinical practice today. The scenario of cardiovascular disease occurrence is rapidly changing. A recent analysis of a large data base in the USA has shown that vascular diseases accounted for more than half of deaths in 1990s, falling to one third in the years 2010–2015 [1]. Accordingly, recent cardiovascular outcome trials in patients with diabetes have reported a much lower incidence of CV events than anticipated.

Behavioral modifications, improvements in acute care and increasing use of preventive therapies such as statins and antihypertensive medications may partly explain these changes [1,5]. In consideration of all the above, it is relevant to document the clinical reality of cardiovascular prevention in more recent cohorts with lower absolute CV risk.

The aim of this study is to document in modern cohorts the degree of control of major CV risk factors and the use of cardioprotective medications in patients with type 2 diabetes (T2DM), managed in different settings - i.e. by specialists at diabetes clinics, or prevalently in primary care; a population-based cohort without diabetes in the same age range is also studied.

2. Subjects, materials and methods

2.1. Study participants

This is a cross-sectional analysis of cardiovascular risk factors in three recent Italian cohorts. We used data collected within the framework of two studies, the TOSCA.IT (Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents Intervention Trial) trial and the Moli-sani study [13,17,18].

TOSCA.IT is a randomized clinical trial designed to compare the impact of Sulphonylureas or Pioglitazone in on add-

on to metformin on cardiovascular outcomes in people with T2DM (<http://www.clinicaltrials.gov>, NCT00700856). Details of the study design have been reported previously [19]. Briefly, the study participants were men and women with T2DM aged 50–75 years recruited at 57 diabetes clinics scattered all over the national territory. By protocol, all patients were treated with oral agents (metformin) and had a glycated hemoglobin between 7 and 9% (53 and 75 mmol/mol). Regular attendance to the clinic was one the inclusion criteria. Key exclusion criteria were acute chronic heart failure, and a serum creatinine concentration greater than 132 μ mol/L. The study was approved by the Ethics Review Committee of the Coordinating Center and of each participating center, written informed consent was obtained from all participants. Participants were recruited between 2008 and 2014. For the purposes of the present analyses only baseline data, collected prior to randomization are used.

The Moli-sani study (NCT03242109) is an ongoing, prospective, observational population-based cohort study of 24,325 individuals (48% men, aged ≥ 35 years, mean age \pm SD: 55.8 \pm 12.0 years) living in the Molise region in south-central Italy. Participants were randomly enrolled from town registries between 2005 and 2010. Briefly, the Moli-sani study was designed to investigate genetic and environmental risk factors for CVD and cancer. Details of the study design have been reported previously [13,18].

The Moli-sani project was approved by the Ethics Committee of the Catholic University in Rome, Italy, written informed consent was obtained from all participants.

To ensure comparability with the TOSCA.IT population we selected among the participants of the Moli-sani study only people in the age range 50–75 treated with oral hypoglycemic agents. Therefore, the study population consists of men and women aged 50–75 years of whom 3028 with non-insulin treated T2DM enrolled in the TOSCA.IT study managed at diabetes clinics; 742 with non-insulin treated T2DM enrolled in the Moli-sani study and managed prevalently in primary care, and 6753 participants of the Moli-sani study without diabetes. Participants were classified as not having diabetes if they had a fasting plasma glucose <100 mg/dL and no current or prior diagnosis of diabetes or use of antidiabetes medications. Data were analyzed according to a cross-sectional observational study design, the analyses were conducted separately for people with or without a prior CV event.

2.2. Measurements

Body weight, height, and blood pressure were measured according to standard procedures for both studies. Body Mass Index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood samples were obtained in the morning after an overnight fast. Biochemistry was performed at the centralized Moli-sani laboratory for the Moli-sani study and at the Department of Laboratory Medicine, Hospital of Desio, for the TOSCA.IT study. Total cholesterol, HDL-cholesterol, triglycerides and high sensitivity C-reactive protein (hs-CRP) were measured by standard methods. LDL-cholesterol was calculated according to the Friedewald equation only for triglyceride values <400 mg/dL; non-HDL-cholesterol was calculated as total cholesterol minus HDL-cholesterol.

Personal and clinical information including education, marital status, smoking habits, and use of medications were collected by questionnaire. The participants were classified as smokers if they were currently smoking one or more cigarettes per day on a regular basis. Prior CV events were defined as self-reported stroke, myocardial infarction, angina, and coronary or extracoronary revascularization procedures, with confirmation by medical records provided during the baseline visit. Recommended treatment targets for LDL-cholesterol and blood pressure were defined according to the guidelines applicable at the time of the study. In particular, for people with diabetes we used the recommendations of the American Diabetes Association [20] (i.e. blood pressure < 130/80 mmHg, LDL-cholesterol < 100 mg/dL in primary prevention, or < 70 mg/dL in secondary prevention) which were issued in 2005 and have remained unchanged up to 2013. For people without diabetes we used the guidelines of the European Society of Cardiology on CV prevention in clinical practice, third joint task force [21] (i.e. blood pressure < 140/90 mmHg, LDL-cholesterol < 115 mg/dL in primary prevention or LDL-cholesterol < 100 mg/dL in secondary prevention) issued in 2004 and applicable through 2012.

2.3. Statistical analysis

The data are presented as numbers and percentages, or mean values and standard deviations as appropriate. Comparison between the study groups were performed with one-factor analysis of variance (ANOVA) and Post-Hoc test for multiple comparisons (Bonferroni Test) for continuous variables, or Chi-square test for categorical variables.

Multivariate general linear model was used to adjust for specific covariates such as sex, age, BMI; adjustment for diabetes duration was also performed when appropriate. The data analysis was generated using SPSS software, version 20 of the IBM System for Windows. A two-sided P-value < 0.05 was considered statistically significant.

3. Results

The general characteristics of the study participants are given in Table 1. The two cohorts with diabetes are comparable with regard to gender distribution, education, marital status and smoking habits. Patients belonging to the clinic-based sample enrolled in the TOSCA.IT trial are slightly, but significantly, younger, have a lower BMI, a higher prevalence of current smoking, shorter diabetes duration and a lower prevalence of prior CVD than those belonging to the Moli-sani study. People with diabetes in both groups are more obese, less educated and smoke less than those without diabetes (Table 1). Prior cardiovascular events were significantly more common among the Moli-sani than the TOSCA.IT diabetic cohort. As expected, non-diabetic people had lower prevalence of prior events as compared to both diabetic cohorts.

Table 2 shows the cardiovascular risk factors profile along with the use of lipid-lowering and antihypertensive medications for the study participants without a prior CV event. There are substantial differences between the two cohorts of patients with type 2 diabetes. Average systolic blood pres-

sure, LDL-cholesterol and non-HDL cholesterol are significantly lower in the TOSCA.IT than in the Moli-sani diabetes cohort. This is probably due to the more frequent use of anti-hypertensive and lipid lowering medications in the TOSCA.IT participants (67.1% vs 60.2% and 54.5% vs 23.6% respectively). Accordingly, the proportion of the cohorts on target for LDL-cholesterol and blood pressure is significantly higher in the TOSCA.IT than in the Moli-sani diabetes cohort, i.e. 47.4% vs 33.4% and 42.6% vs 9.5%, respectively, (Fig. 1, panel A). It is however of note that the management of blood pressure and plasma lipids remains far from optimal also in the TOSCA.IT population with more than 50% of the cohort off target for LDL-cholesterol and nearly 60% off target for blood pressure (Fig. 1, panel A). As for people without diabetes, they have significantly higher LDL-cholesterol and non-HDL, but significantly lower triglycerides and C-reactive protein values than diabetes participants in both cohorts (Table 2). The treatment target for LDL-cholesterol is achieved by 29.5% of the non-diabetes cohort, this is a significantly lower proportion as compared to people with diabetes in both cohorts (Fig. 1, panel A); for blood pressure the proportion on target is 47.4%, i.e. higher than in people with diabetes in both cohorts (Fig. 1, panel A). Notwithstanding the high proportion of people off target for LDL-cholesterol and blood pressure the use of lipid-lowering, and antihypertensive medications in people without diabetes is remarkably low (6.7% and 30.8%, respectively), and definitely lower than in people with diabetes (Table 2).

Data relative to the participants with a prior CV event are given in Table 3 and Fig. 1, panel B. People with diabetes managed at diabetes clinics, as compared to those managed in primary care, show significantly lower LDL-cholesterol and blood pressure values, a more frequent achievement of the recommended treatment targets for LDL-cholesterol (26.8% vs 15.1%) and blood pressure (43.8% vs 8.5%) and a more frequent use of lipid lowering and antihypertensive medications (84.5% vs 66.0% and 89.9% vs 79.6%, respectively). For people without diabetes the treatment targets for LDL-cholesterol and blood pressure are achieved more frequently than in people with diabetes (Fig. 1 panel B), the proportion remains however low (i.e. <50%) and the use of antihypertensive and lipid-lowering medication, though considerably higher than in the cohort without CVD, remains far from optimal. It is also relevant to underline that a substantial proportion of people in secondary CV prevention, with or without diabetes, continue to smoke (Table 3).

4. Discussion

The study provides updated evidence on the management of cardiovascular risk factors in cohorts with different absolute CV risk (i.e., with or without diabetes, with or without a prior CV event). The results show that a large proportion of the study participants with or without diabetes does not achieve the recommended treatment targets for blood pressure and LDL-cholesterol and that the use of antihypertensive and lipid-lowering medications is suboptimal, both in primary and secondary CV prevention. This applies to the setting of primary care and specialistic care as well, however patients

Table 1 – General characteristics of the participants.

	Diabetes		P	No Diabetes	P vs Diabetes TOSCA.IT	P vs Diabetes Moli-sani
	TOSCA.IT	Moli-sani		Moli-sani		
N	3028	742		6753		
N (% men)	1778 (58.6)	295 (39.8)	<0.0001	4076 (60.4)	0.11	<0.0001
Age (years)	62.6 ± 7.4	63.6 ± 6.4	<0.0001	60.2 ± 6.9	<0.0001	<0.0001
BMI (Kg/m ²)	30.3 ± 4.5	31.0 ± 5.4	<0.0001	27.9 ± 4.5	<0.0001	<0.0001
Education						
Up to lower secondary school	2084 (68.8)	520 (70.1)	0.24	3807 (56.4)	<0.0001	<0.0001
High school or higher	945 (31.2)	222 (29.9)		2942 (43.6)		
Marital Status N (%)						
Single/Widowed	479 (15.8)	109 (14.7)	0.39	897 (13.3)	0.001	0.27
Married/Cohabiting	2551 (84.2)	633 (85.3)		5854 (86.7)		
Smoking N (%)						
Current smoker	533 (17.6)	103 (13.9)	0.017	1487 (22.0)	<0.0001	<0.0001
Non smoker	2497 (82.4)	639 (86.1)		5266 (78.0)		
Diabetes duration (years)	8.5 ± 5.7	8.9 ± 7.0	<0.0001	–		
With Prior CV events N (%)	258 (8.5)	98 (13.2)	<0.0001	273 (4.0)	<0.0001	<0.0001

Table 2 – Cardiovascular risk factors profile and use of antihypertensive and lipid lowering medications for the participants without a prior CV event.

	Diabetes		P*	No Diabetes	P [§] vs Diabetes TOSCA.IT	P [§] vs Diabetes Moli-sani
	TOSCA.IT	Moli-sani		Moli-sani		
N	2747	642		6469		
Systolic Blood Pressure (mmHg)	134.0 ± 14.6	151.0 ± 19.7	<0.0001	142.8 ± 19.6	<0.0001	<0.0001
Diastolic Blood Pressure (mmHg)	79.6 ± 8.3	82.7 ± 8.8	<0.0001	82.8 ± 9.3	<0.0001	<0.0001
HDL-cholesterol (mg/dL)	46.8 ± 12.6	51.1 ± 13.2	<0.0001	59.2 ± 14.9	<0.0001	<0.0001
LDL-cholesterol (mg/dL)	104.0 ± 31.5	115.8 ± 35.1	<0.0001	133.3 ± 33.4	<0.0001	<0.0001
Triglycerides (mg/dL)	151.6 ± 82.3	160.4 ± 88.9	<0.0001	120.1 ± 65.0	<0.0001	<0.0001
Non-HDL cholesterol (mg/dL)	134.1 ± 36.6	147.1 ± 38.4	<0.0001	157.1 ± 36.7	<0.0001	<0.0001
Hs-C-Reactive Protein (mg/L)	3.65 ± 7.80	3.41 ± 4.15	<0.0001	2.42 ± 2.86	<0.0001	<0.0001
On lipid lowering medications (%)	54.5	23.6	<0.0001	6.7	<0.0001	<0.0001
On antihypertensive medications (%)	67.1	60.2	<0.0001	30.8	<0.0001	<0.0001
Current smokers (%)	17.7	14.5	0.10	22.4	<0.0001	<0.0001

*Multivariate General Linear Model (GLM) adjusted for age, sex, BMI and diabetes duration.

§ Multivariate General Linear Model (GLM) adjusted for age, sex and BMI.

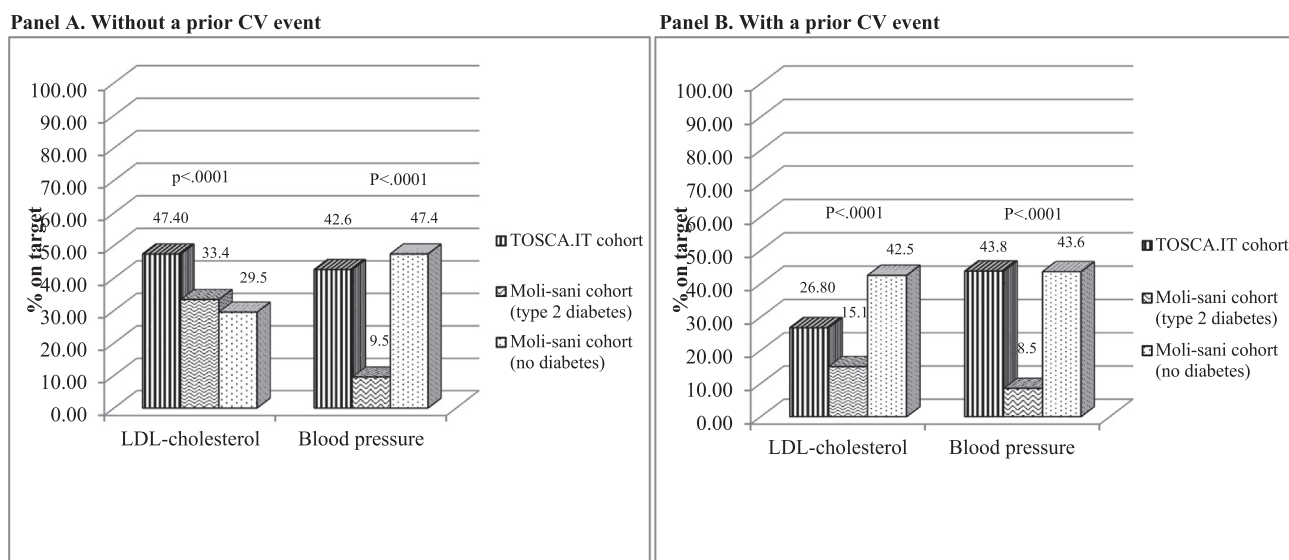


Fig. 1 – Proportion of participants achieving the recommended treatment targets for LDL-cholesterol and blood pressure in the cohort without a prior CV event (Panel A) or with a prior CV event (Panel B). According to the standards of care of the American Diabetes Association, the recommended treatment targets in people with diabetes were LDL-c < 100 mg/dL in primary prevention, or < 70 mg/dL in secondary prevention, and blood pressure < 130/80 mmHg in primary and secondary prevention (20). According to the ESC guidelines, the recommended treatment targets in people without diabetes were LDL-c < 115 mg/dL in primary prevention, or < 100 mg/dL in secondary prevention, and blood pressure < 140/90 mmHg in primary and secondary prevention (21).

with diabetes regularly attending diabetes clinics achieve a better control of LDL cholesterol and blood pressure as compared to both diabetic patients managed mainly in primary care and people without diabetes.

Audits of clinical practice may help improving the level of care by providing an objective assessment of the extent to which the guidelines are implemented in clinical practice [22]. The study results highlight the relevance of the model of diabetes care, as it is known that adherence to guidelines is associated with better prognosis [5,8,12,16]. A structured model of care such as that of the diabetes clinics which provides continuity of care through regular scheduling of follow-up and a comprehensive therapeutic approach including patient education and empowerment, can improve patient's adherence to lifestyle modifications and drug therapies in the medium and long term and can bear on outcomes [8,14,16,23]. To the contrary an unstructured, mainly “on demand” model of care, such as that of the primary care, is associated with poorer intensification of treatment and likely with lower adherence to treatment, particularly with regard to blood pressure control. Yet considerable problems remain in the achievement of treatment targets for blood pressure and LDL-cholesterol, control of body weight and quitting smoking also within the context of diabetes care provided at diabetes clinics, thus highlighting the potential for further improvement. Furthermore, considering that other chronic conditions, beside diabetes, require regular monitoring, the study results suggest that potential inadequacies in the quality of care may also be experienced by other population groups.

Prior studies have repeatedly documented the insufficient implementation of cardiovascular prevention guidelines in

populations with or without diabetes. They are however mostly based on older cohorts and have focused mainly on high risk groups [11–13]. Due to differences in the selection criteria for the study participants and the continuous updating of treatment goals, the comparison with existing studies is not straightforward. In a study undertaken in the years 2004–2006 at 10 large hospital-based out-patients diabetes clinics in Italy, patients with type 2 diabetes and no prior CV events had average LDL-cholesterol of 130 mg/dL and blood pressure of 140/80 mmHg, 22% were currently smoking and only 26% of the cohort was on statins [11]. In the EUROASPIRE II survey conducted in the years 1999–2000 in 15 European countries, average LDL-cholesterol and blood pressure values in patients with diabetes and overt CHD were respectively, 114 mg/dL and 142 mmHg [24]. A recent study on German cohort indicates that treatment targets for major CV risk factors are largely unmet in the general population [25]. On the overall our results document a better control of blood pressure and LDL-cholesterol in people with or without diabetes as compared to prior studies [11–13,24,26–28], but at the same time they underline the potential for further improvement.

Some study limitations must be taken into account when interpreting data. We acknowledge that, due to the inclusion criteria relative to age and diabetes treatment (i.e. oral agents only), the selected cohorts are not fully representative of the general population of people with diabetes, yet these patients are the large majority of people with diabetes in clinical practice. A recent report of the Center for Disease Control estimates that 60% of the 23 million adults in the U.S. with diagnosed diabetes in 2015 were younger than 65 years and relatively free of complications [29]; the analysis of a large Italian database suggests that in Italy nearly 70% of the

Table 3 – Cardiovascular risk factors profile and use of antihypertensive and lipid lowering medications for the participants with a prior CV event.

	Diabetes		P*	No Diabetes	P [§] vs Diabetes TOSCA.IT	P [§] vs Diabetes Moli-sani
	TOSCA.IT	Moli-sani		Moli-sani		
N	281	100		284		
Systolic Blood Pressure (mmHg)	134.0 ± 14.9	152.4 ± 18.8	<0.0001	144.8 ± 19.7	<0.0001	<0.0001
Diastolic Blood Pressure (mmHg)	79.0 ± 8.8	80.1 ± 9.6	0.005	80.8 ± 9.2	0.012	0.003
HDL-cholesterol (mg/dL)	42.9 ± 10.0	49.2 ± 11.7	<0.0001	53.2 ± 13.7	<0.0001	<0.0001
LDL-cholesterol (mg/dL)	90.3 ± 32.1	99.2 ± 28.3	0.079	109.1 ± 34.6	<0.0001	0.002
Triglycerides (mg/dL)	162.3 ± 83.7	152.5 ± 84.5	<0.0001	129.5 ± 62.1	<0.0001	0.001
Non-HDL cholesterol (mg/dL)	122.8 ± 37.3	129.4 ± 32.9	0.058	134.7 ± 38.2	0.001	0.037
Hs-C-Reactive Protein (mg/L)	2.94 ± 5.16	2.86 ± 4.02	0.21	2.61 ± 3.04	0.16	<0.0001
On lipid lowering medications (%)	84.5	66.0	<0001	55.1	<0.0001	0.015
On antihypertensive medications (%)	89.9	79.6	0.014	63.4	<0.0001	<0.0001
Current smokers (%)	16.7	10.2	0.073	12.8	0.22	0.43

*Multivariate General Linear Model (GLM) adjusted for age, sex, BMI and diabetes duration.

§ Multivariate General Linear Model (GLM) adjusted for age, sex and BMI.

patients with diabetes are treated with oral agents [30]. Therefore, the study findings are indicative of the real-life clinical practice in Italy and suggest that it may be worthwhile to evaluate the adequacy of the quality of care for other silent chronic conditions which, like diabetes, require regular scheduling of follow-up visits. Furthermore, self-motivation and willingness to attend regular follow-up could be a possible bias leading to better outcomes in people enrolled in the TOSCA.IT study. Finally, the definition of primary or secondary prevention cohorts was based on self-reporting of prior CV events supported by clinical documentation but the events were not adjudicated.

In conclusion, the study documents that in modern cohorts a large proportion of the study participants with or without diabetes does not achieve the treatment targets for LDL-cholesterol and blood pressure, both in primary and secondary CV prevention. People with diabetes attending diabetes clinics are more intensively treated and achieve a better control of major CV risk factors than those managed in primary care, thus highlighting the relevant role of a structured model of care for the management of the complexity of the disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributors

OV, LI, GR, MBD, GdG, AAR contributed to the conception and design of the work, and interpretation of data. SC and ADC managed data collection of the Moli-sani Study. MV and MM, managed data collection of the TOSCA trial. MV, SC, MM analyzed the data. OV, LI wrote the manuscript. GR, MBD, GdG, AAR, originally inspired the research and critically reviewed the manuscript.

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