Metformin Use is Associated with Reduced Incidence of Invasive Pneumococcal Disease after a Pneumococcal Vaccine in Adults with Type 2 Diabetes: A Retrospective Cohort Study

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Background

- Metformin is a first-line agent for type 2 diabetes (T2DM)
- Metformin has also been shown to have immunomodulating properties in vaccine responses, chronic inflammation, and various infectious diseases[1,2]
- Few studies address metformin's role in prevention of invasive pneumococcal (IPD) or vaccine effectiveness

Objective

- To determine whether metformin-use is associated with lower risk for IPD post receipt of a pneumococcal vaccine (PNV) in those with and without T2DM

Methods

- Study Design: retrospective U.S. cohort analysis of a third-party medical and pharmacy claims database from 2009 – 2019

Inclusion Criteria:
- Adults ≥ 18 years
- Receipt of a PNV within the study period
- Continuously enrolled in benefits ≥ 1 year before and after a PNV

Definitions/Outcome:
- Primary outcome: IPD was evaluated from day 14 to day 365 post PNV (index date)
- IPD was determined using ICD-9/10-CM codes: A40, A40.3, A40.8, A40.9, A41.9, J13, J15.4, J159, J16, J16.8, J17, J18, R65.2, R65.20, R65.21, 995.92, 995.91, 484, 486, 481-483, 38.2, 38
- Metformin-use: ≥ 90-day supply filled prior to PNV

Statistics:
- Comparisons of IPD between groups were analyzed using Wilcoxon Rank Sum and Chi-squared tests
- Multivariable logistic regression models were conducted
- Covariates adjusted for were age, sex, vaccine type, year, and comorbidities
- Statistics were run using SPSS version 25.0 (IBP Corp, Armonk, NY)

Results

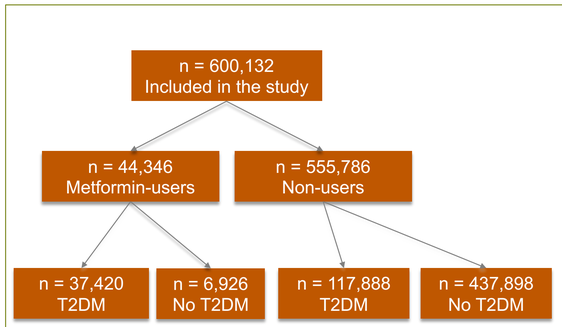

Figure 1: Flow diagram of cohort flow.
PNV = pneumococcal vaccine; T2DM = type 2 diabetes mellitus.

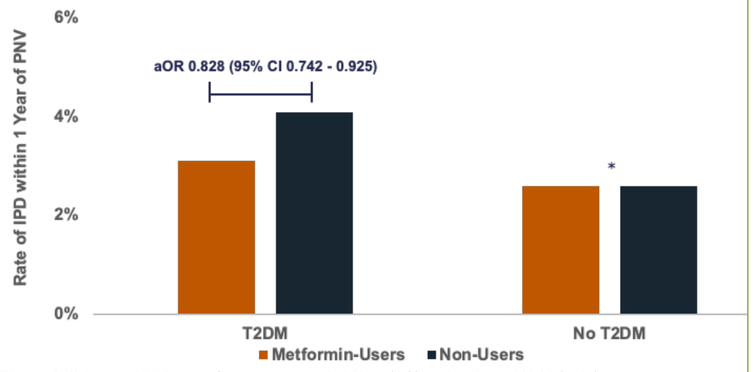

Figure 2: IPD post PNV in metformin-users with T2Dm (left) and without T2DM (right)
*There was no difference of IPD among metformin-users without T2Dm [aOR 0.989 (95% CI 0.852 – 1.148)]. Comparisons were analyzed using multivariable logistic regression models adjusted by age, sex, vaccine type/date, and comorbidities. IPD = invasive pneumococcal disease; T2DM = type 2 diabetes mellitus; aOR = adjusted odds ratio.

Table 1: Cohort characteristics of metformin-users vs. non-users stratified by metformin-use and T2DM status

	T2DM (n=155,308)			No T2DM (n=444,824)		
	Metformin-user (n=37,420)	Non-user (n=117,888)	P-Value	Metformin-user (n=6,926)	Non-user (n=437,898)	P-Value
Age, median (IQR)	62 (55-69)	65 (57-72)	**0.001**	63 (56-69)	66 (59-72)	**0.001**
Sex			0.001			0.001
Male	18,423 (49.2%)	60,845 (51.6%)		3,337 (48.2%)	190,895 (43.6%)	
Female	18,997 (50.8%)	57,043 (48.4%)		3,589 (51.8%)	247,003 (56.4%)	
Vaccine Type			**0.001**			**0.001**
PPSV23	18,053 (48.2%)	52,503 (44.5%)		3,209 (46.3%)	161,500 (36.8%)	
PCV13	19,367 (52.8%)	65,385 (56.5%)		3,717 (53.7%)	276,398 (63.2%)	
Comorbidity						
CKD	58 (0.2%)	801 (0.7%)	**0.001**	4 (< 0.1%)	878 (0.2%)	**0.009**
COPD	1,939 (5.2%)	6,097 (5.2%)	0.831	226 (3.3%)	24,919 (5.7%)	**0.001**
HIV	206 (0.6%)	576 (0.5%)	**0.001**	29 (0.4%)	5,277 (1.2%)	**0.001**
Splenectomy	20 (0.1%)	87 (< 0.1%)	0.195	3 (< 0.1%)	707 (0.2%)	**0.017**
BMT	0 (0%)	55 (< 0.1%)	**0.001**	0 (0%)	433 (< 0.1%)	**0.010**
Liver Disease	8 (< 0.1%)	30 (< 0.1%)	0.666	2 (< 0.1%)	114 (< 0.1%)	0.855
Heart Disease	145 (0.4%)	658 (0.6%)	**0.001**	12 (0.2%)	1,539 (0.4%)	**0.016**

T2DM = type 2 diabetes mellitus; PPSV23 = 23 valent pneumococcal polysaccharide vaccine; PCV13 = 13 valent pneumococcal conjugate vaccine; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; BMT = bone marrow transplant; HIV = human immunodeficiency virus

- Among T2DM metformin-use was independently associated with lower risk of IPD after adjusting for age, sex, comorbidities, and vaccine
- Among no T2DM, metformin-use was not independently associated with IPD risk
- Median (IQR) days to IPD post PNV was 200 (107 – 282) in the metformin-users vs. 182 (99 – 274) in non-users

Discussion

Strengths:
- Large study > 600,000
- Novel data evaluating metformin and PNV effectiveness against IPD

Limitations:
- Retrospective study prone to bias
- Did not assess medication adherence, vaccination history, disease severity or mortality
- Did not assess long term outcomes, long-term metformin use, and other demographics and conditions other than T2DM

Conclusions

Among persons with T2DM, chronic metformin-use prior to PNV was associated with a 17% lower risk of IPD within 1 year.

These results add to the sparse data highlighting the immunomodulatory effects of metformin and its potential role in vaccine-care, aging, and preventative medicine

References:
1. Chen X, Guo H, Qiu L, et al. Frontiers in Immunology. 2020:2056.
2. Frasca D, Diaz A, Romero M, Blomberg BB. Frontiers in Aging. 2021:30.

Conflicts of interest declaration: none