Research

BMJ Global Health

The impact of a cash transfer programme on tuberculosis treatment success rate: a quasi-experimental study in Brazil

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OBSERVATIONAL STUDIES IN ACTION

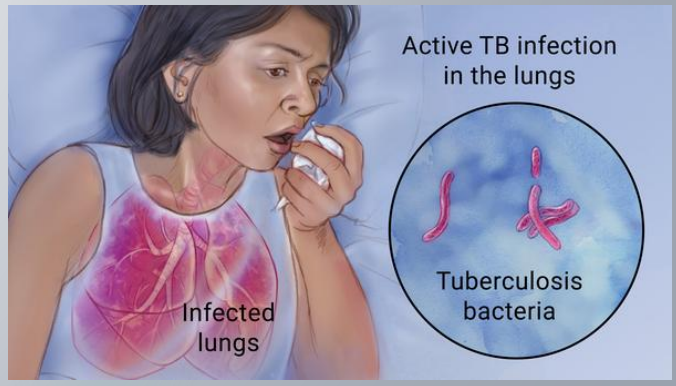
PQHS 500

2020-04-02

JESUS GUTIERREZ

Tuberculosis

- Caused by *Mycobacterium tuberculosis* (Mtb)
- Top cause of death due to infectious disease globally
- Two million deaths and 9 million new cases per year
- Transmitted through the air
- If untreated, TB disease has a mortality rate of 50%



Brazil

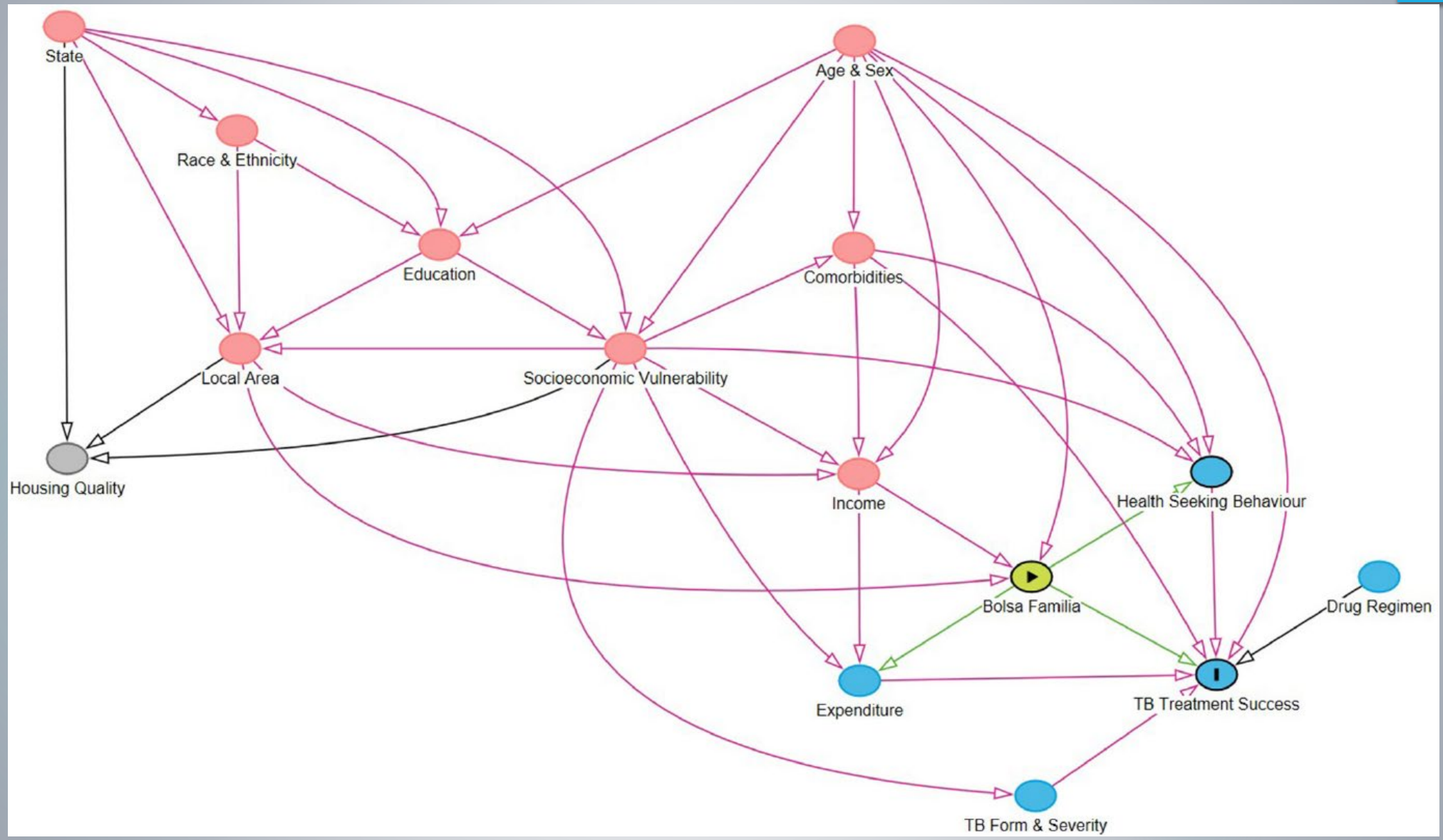
- In 2018,
  - 95,000 new cases (68% men, 30% women, 2% children) – 45 cases/100,000 individuals
  - 6,700 deaths (including 1,900 among people with HIV)
- TB treatment coverage at 87%
- Treatment success rate at 71%

Source: WHO

Background

- Limited evaluation of social protection intervention for TB prevention, care and control.
- Bolsa Familia Programme (BFP) is one of the largest conditional cash transfer programs in the world.
- **Study aims**:
  1. Use propensity score matching to create a control group balanced for propensity to receive BFP
  2. Provide an estimate of the average treatment effect of BFP on TB treatment success rate among recipients
  3. Reflect on the utility of the resulting estimate for changing TB policy

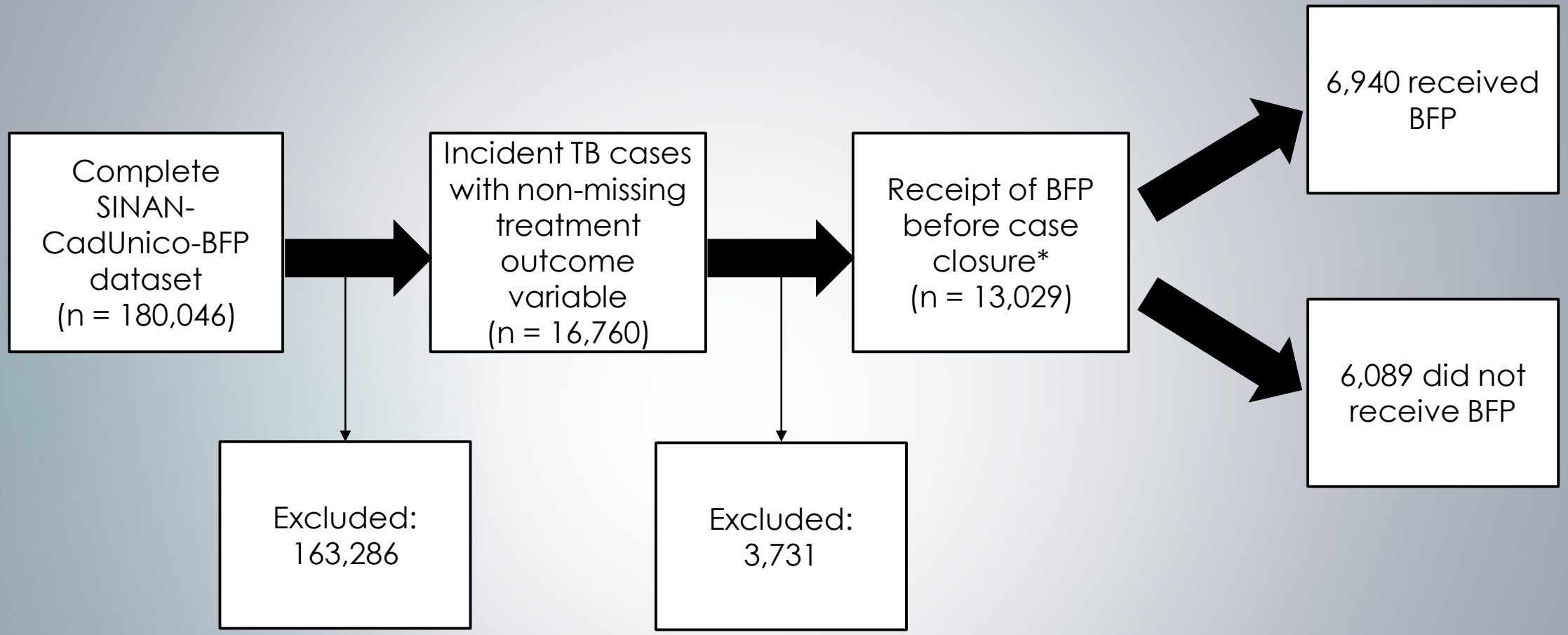
Conceptual Framework



Methods

- Linkage of two datasets
  - 2010 TB dataset from SINAN (Notifiable Disease Surveillance System)
  - 2011 CadUnico dataset – registry of all low-income Brazilian families
    - Contains BFP payroll information
- Exposure: Variable monthly stipend received from BFP
- Outcome: Completion of TB treatment

Study Flow Diagram

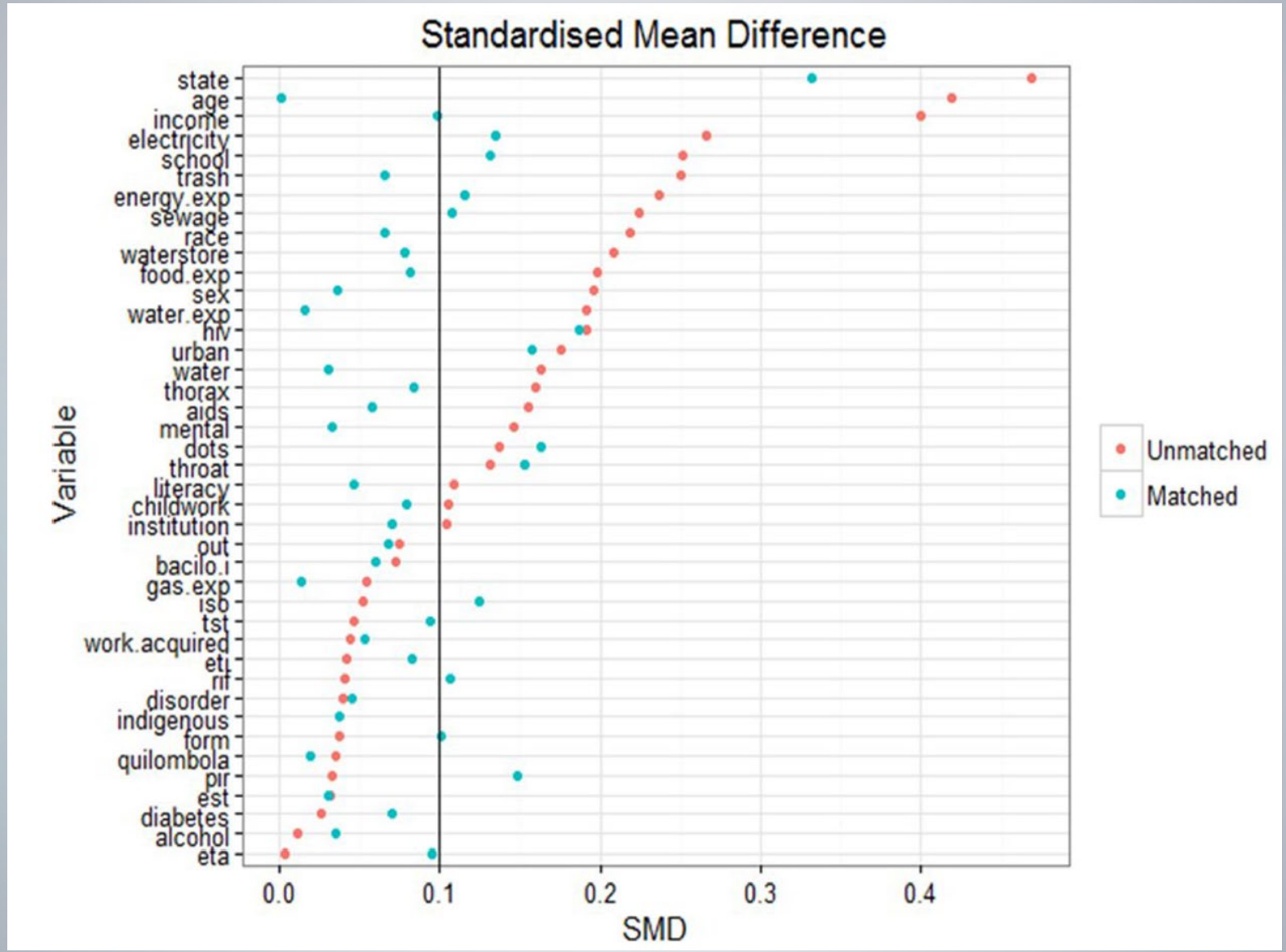


*Case closure: date on which an outcome is recorded

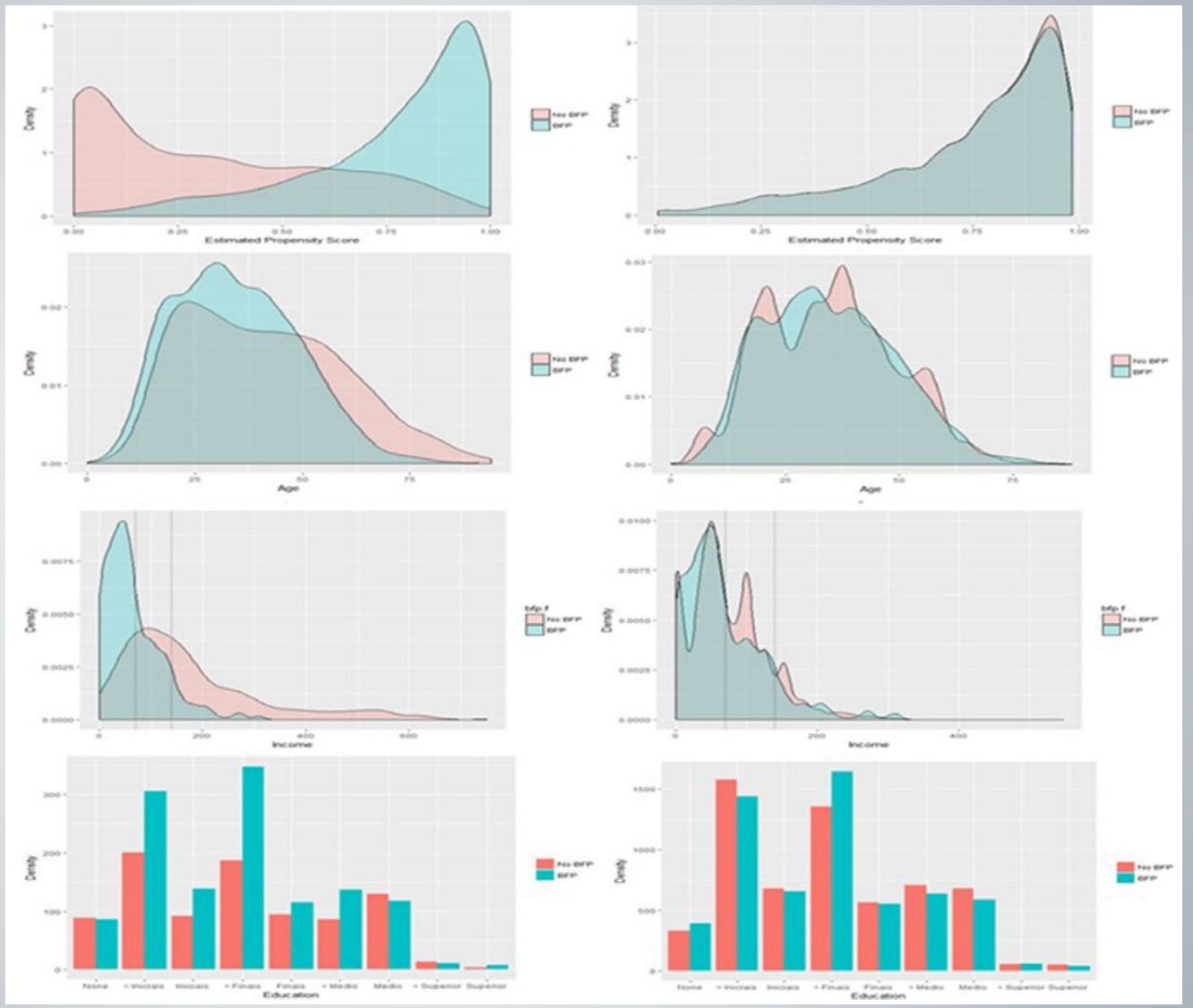
Propensity Score Matching

- Used 45 covariates
- Done with replacement and multiple matches to minimize bias and variance
- Used a caliper of 0.1 SD from the mean propensity score
- Multiple matches were weighted to form one matched control for each patient
- Used complete cases: 2,167 individuals at 50% missing data threshold and 3,048 individuals at 25% threshold.

Standardized Mean Difference



Similarities between Groups after Matching



Estimating Effect of BFP

- Using average effect of treatment on the treated (ATT)

Table 2 Results of propensity score matching estimates of the ATT for four models

Models* n controls=898 n exposed=1269	ATT	95% CI	Controls matched (unweighted), n	Exposed dropped, n	Pairs matched (weighted), n	Unique controls, n
Model A†	10.58	(4.39 to 16.77)	6021	109	1160	545
Model B‡	7.21	(1.33 to 13.09)	6468	21	1248	656 (D2)

Models* n controls=1319 n exposed=1729	ATT	95% CI	Controls matched (unweighted), n	Exposed dropped, n	Pairs matched (weighted), n	Unique controls, n
Model C*	6.31	(1.46 to 11.16)	8895	70	1659	955
Model D*‡	7.06	(2.57 to 11.56)	9272	17	1712	1001

Discussion

- Among those who received BFP, all models showed substantial absolute increase in TB treatment success rate (6.3% to 10.6%)
- Impact may be higher in settings with lower baseline treatment success rates
- Profiles of TB patients who received BFP was not dissimilar to those who did not receive BFP
  - Shared vulnerability not captured by current BFP targeting and enrollment process

Limitations

- Did not consider dose-response relationship and assumed that receipt of any amount of financial assistance for any amount of time was enough
- Assumed that exposure received by one individual did not affect the outcome of others (although they could be living in same household, be relatives or members of the same community).
- Used a dichotomous outcome variable which did not capture full extent of potential results
- Did not consider loss to follow-up and transferred cases.

Questions?

THE IMPACT OF A CASH TRANSFER PROGRAMME ON TUBERCULOSIS TREATMENT SUCCESS RATE: A QUASI-EXPERIMENTAL STUDY IN BRAZIL

AMIN SAAD, MD

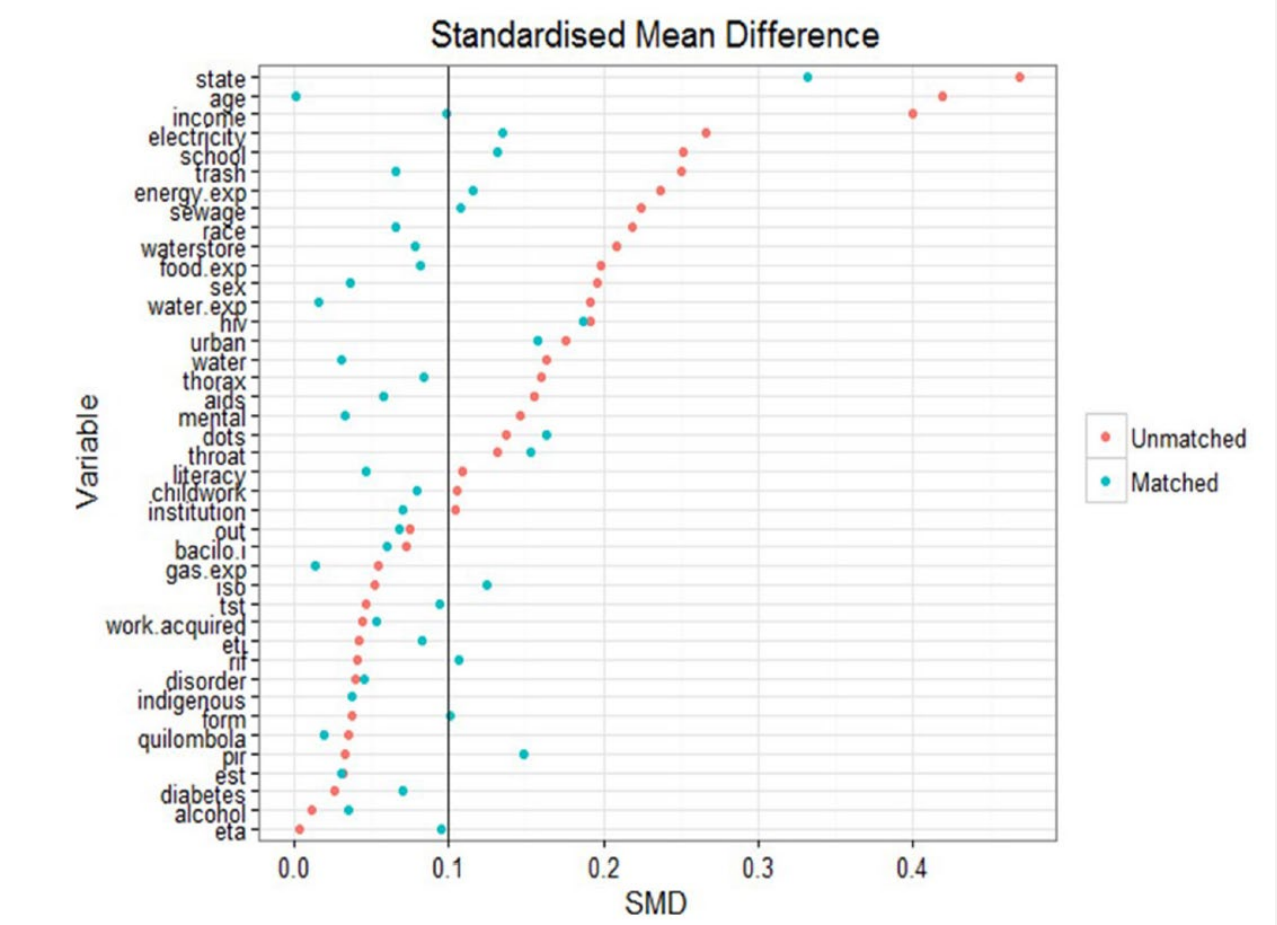
OSIA – SECOND READER

PQHS 500

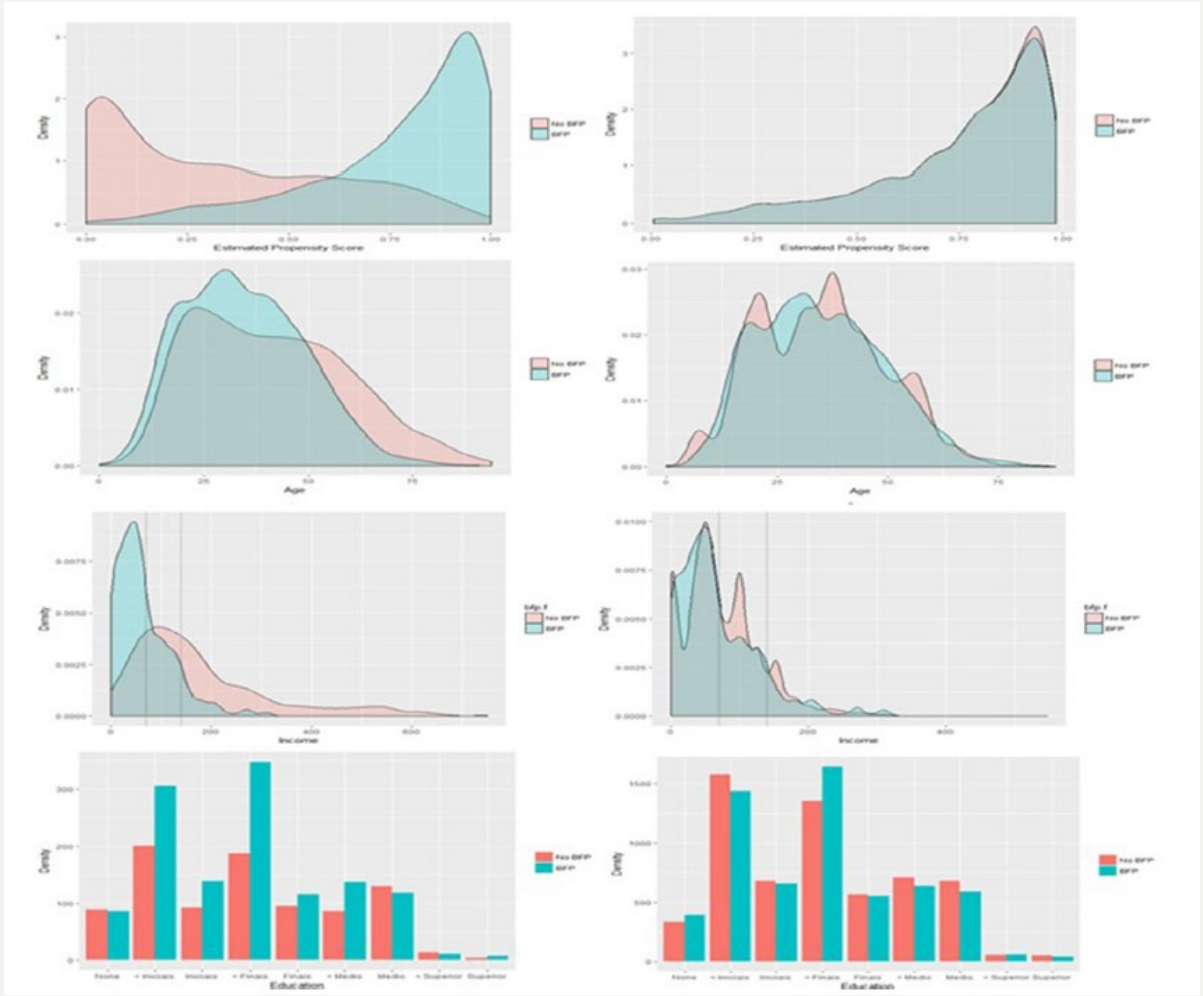
SUMMARY

- Background: Social protection policies such as Brazil's Bolsa Familia Programme (BFP) may play a role in tuberculosis (TB) elimination
- Aim: evaluate the effect of BFP on TB treatment success rate
- Method:
  - Data from Brazil's TB notification system (SINAN) was linked to the national poverty registry(CadUnico)
  - Propensity score weighted matching with replacement using R match and the MatchIt package
  - Exposure patients receiving BFP, outcome case closure (treated, successful completion of Rx , death)
- Main finding:
  - Patients with TB enrolled in BFP are more likely to complete their treatments successfully [range based on method from 7 to 10% difference)

HOW GOOD IS THE BALANCE AFTER MATCHING?



OVERLAP PLOTS SHOW 3 RANDOM VARIABLES TO SUGGEST BALANCE, WHAT ABOUT THE REST?



ESTIMATE OF THE BFP ON TB TREATMENT

- 50% missing vs 25% missing variable threshold
- Multiple imputation (ATT 7.22 appendix 2)
- NNT 1 for every 9 patients

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STRENGTHS AND LIMITATIONS

1. Utilization of quasi-experimental approaches
2. Risk of bias is minimized with careful use of a DAG (directed acyclic graph)
3. Comparability of the control group
4. Possibility of drawing causal conclusions
    1. Positivity (inaccurate income threshold)
    2. Consistency (further work need to assess dose-response relationship)
    3. Conditional exchangeability
    4. Non-interference
5. Limitations: quality of data (missingness), non-logitudinal data, composite outcome

DISCUSSION

- *" … While the findings of this study are consistent with what observed in the literature, conclusions are hampered by the potential biased nature of the control group."*
  - *"we wish to achieve a 'balance' in these values , which may approximate the balance produced by a conventional randomized procedures"*
- *Linkage between two datasets that are 1 year apart?*
- *Missing completely at random*
- *"A sensitivity analysis was run …"*
  - *"ATT was also estimated by a multiple imputation-based sensitivity analysis"*
- *Using all variables in the set to create a propensity score?*
- *"The CIs thus account for the uncertainty due to the matching procedure, but do not account for the uncertainty due to the fact that the estimated propensity score is itself a function of the data; the latter feature leads to conservative inferences.*

OSIA Presentation

April 2, 2020

Laurie Ann Moennich, MPH, CPH

Cleveland Clinic

Cantillon et al. (2018)

Comparative study of acute and mid-term complications with leadless and transvenous cardiac pacemakers

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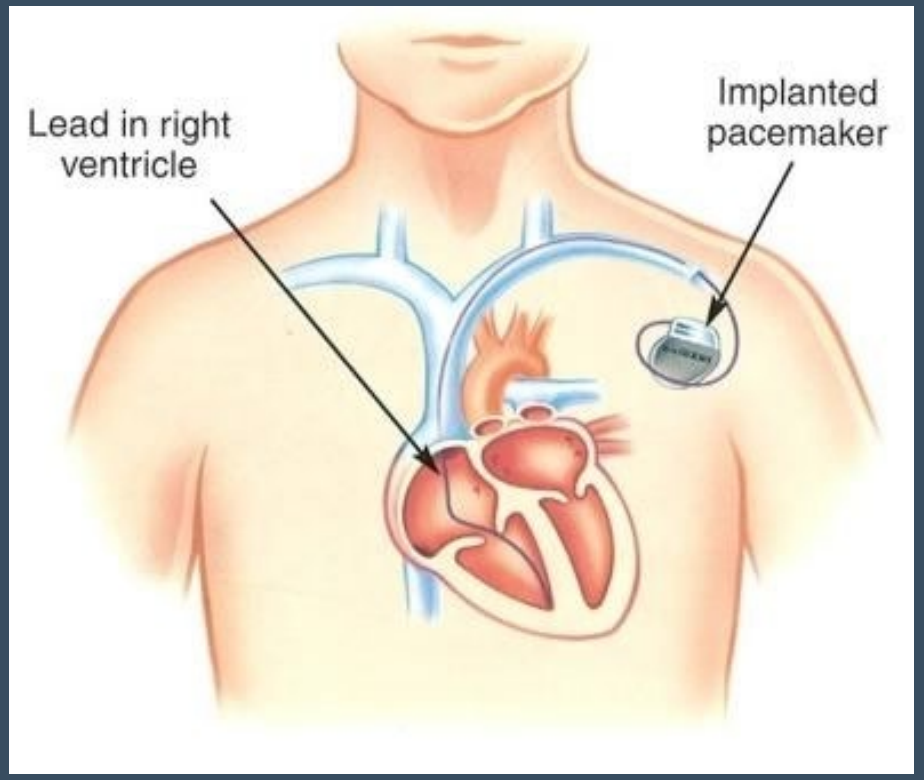
Background

- Leadless cardiac pacemakers (LCPs) aim to reduce lead and pocket-related complications seen with transvenous pacemakers (TVPs)

Transvenous pacemakers (TVPs)



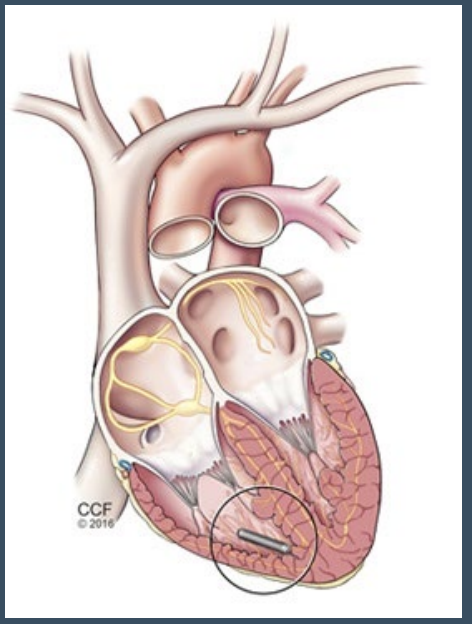
- ~ 1 million TVPs are implanted annually around the world
- Reliable, familiar technology
- Implantation technique requires the pulse generator to be implanted in a subcutaneous pocket

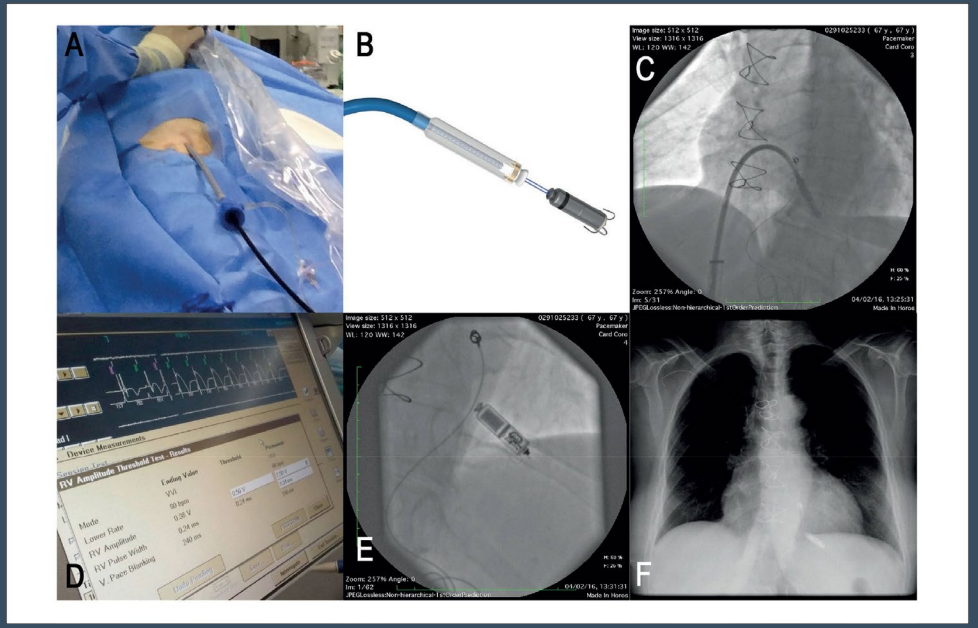
- Acute complications:
  - Pneumothorax, hemothorax, cardiac performation, pocket hematoma, lead dislodgement

- Long term complications:
  - Early battery depletion, lead fracture, incomplete capture, tricuspid valve regurgitation, infection

Leadless pacemakers (LCPs)

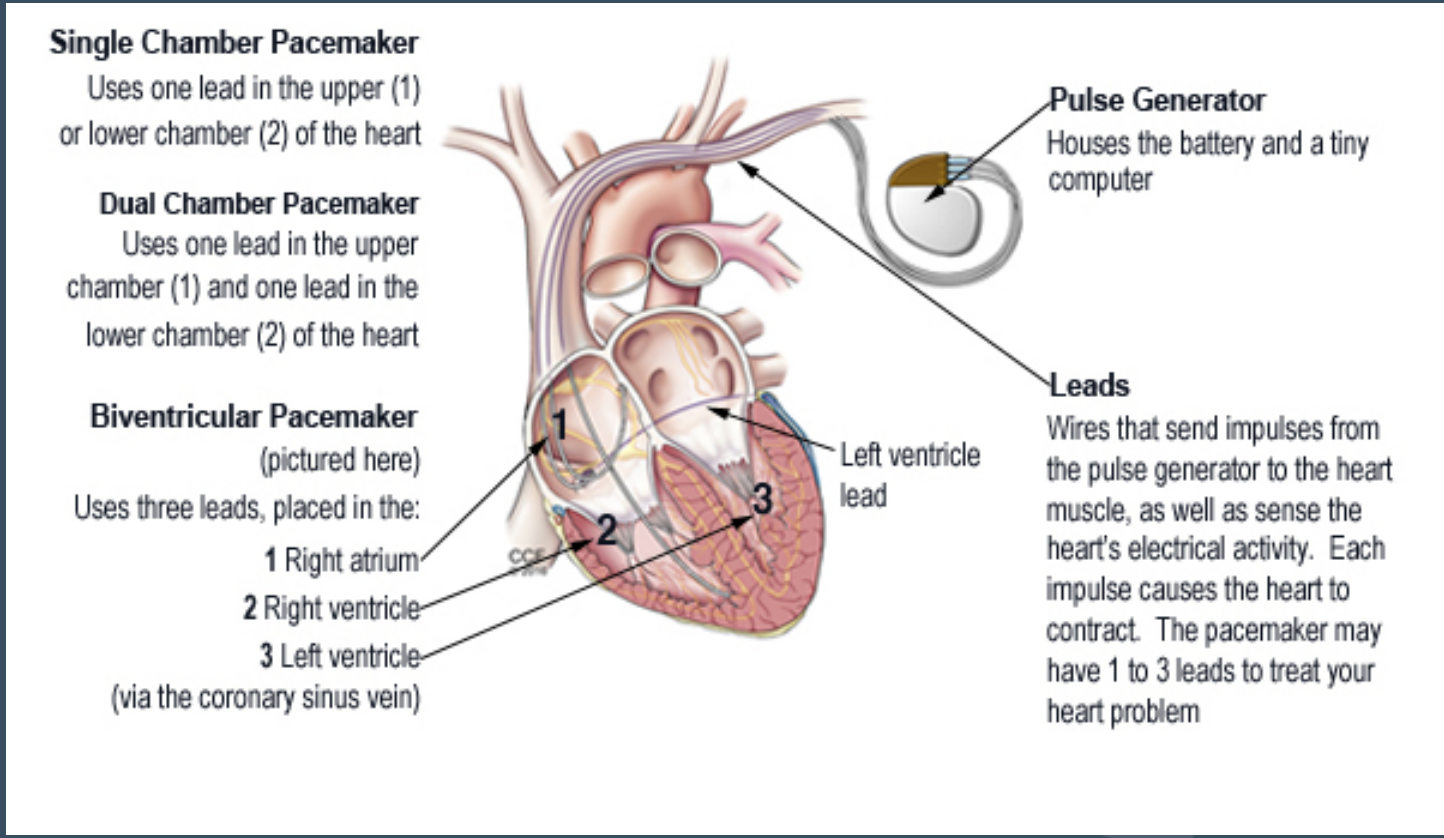
- Relatively new (and exciting!) to the EP world
- No need for a subcutaneous pocket
- No leads
- Very small (~1cm^3)
- Self contained unit delivered through a transfemoral venous catheter and affixed into the right ventricle
- Complications minimized





Can we compare LCPs and TVPs?

- Direct comparison of adverse events is limited by differences in patient populations/characteristics
  - Leadless pacemakers are typically indicated for patients who need single ventricle pacing versus TVPs (can include single, dual, and CRT pacing)
- Comparisons also limited by study design



Methods

- Short term and long term AEs from the Nanostim LCP are compared with conventional single chamber TVPs
  - Safety data from extended follow up of Leadless IDE trial
  - TVP data is from US insurance claims database

Leadless Pacemaker IDE Trial

- Patients implanted with Nanostim LCP
  - Feb. 1, 2014-Jan. 31, 2016
  - Follow up 2 wks, 6wks, 3 months, 6 months
    - Every six months till end of study.
  - Primary safety endpoint:
    - Freedom from serious adverse device event (SADE) @ 6mo post implant
    - SADE is classified as any untoward event that is related to the device or procedure
      - “serious” = led to death, life-threatening illness or injury, permanent impairment, hospitalization, and/or medical intervention

TVP Data

- Extracted from Truven Health MarketScan Research Database
  - 20 billion de-identified, person specific insurance claims from ~350 US private sector payers
- Commercial Claims and Encounters Database combined with Medicare Supplemental Database
- Patients 18 years or older
  - Implanted with single-chamber pacemaker from any manufacturer
  - ICD-9 code 37.81, 37.82 or CPT code 33207
  - Relevant co-morbidities collected from medical history prior to implant
    - atrial fibrillation, hypertension, dia- betes, coronary artery disease, vascular disease, tricuspid valve disease

TVP Data – Safety Data

- Complications collected from inpatient and outpatient billing codes recorded from date of implantation onward
  - Infection (device-related infection, endocarditis)
  - Thoracic trauma (pneumothorax and hemothorax from lead insertion)
  - Pocket complications (hematoma, pocket revision)
  - Electrode dislodgement
  - Venous embolism or thrombosis
  - Cardiac perforation
  - Generator complications
    - Generator explants (within 30 days = acute, within 18 months = mid-term (earlier than expected))
  - Multiple codes from the same event were counted as a single event (ex. Device infection and extraction would be one event).

Methods (cont.) - Comparisons

- Subset of TVP patients with similar comorbidities to LCP cohort was identified.
- 2:1 propensity score matching
  - Nearest-neighbor method without replacement
- 2:1 ratio was the highest ratio for which resulting groups were well-matched on all baseline parameters
- Covariates: age, sex, and relevant baseline comorbidities including atrial fibrillation, coronary artery disease, diabetes, hyperlipidemia, hypertension, tricuspid valve disease, and peripheral vascular disease.
- Primary outcome: overall freedom from complications
- Secondary outcome: proportion of long/short term events between groups

Statistical Analysis

- Continuous variables – Student's t test
- Categorical variables – Chi-squared test
- Proportions compared - Fisher exact test
- Event rates compared - Poisson regression
- Freedom from complications – Kaplan-Meier method and compared between TVPs and LCPs using weighted Cox proportional hazards regression
  - Adjusted for age, sex, and baseline comorbidities
- R (🥰!!!) Version 3.1.1:
  - survival
  - MatchIt
  - coxphw

Baseline Demographic Characteristics

Table 1 Baseline demographic characteristics of propensity score–matched patients

Characteristic	Patients with leadless pacemaker (n = 718)	Patients with transvenous pacemaker (n = 1436)	*P*
Age (y)	75.6 ± 11.9	76.1 ± 12.3	.39
Follow-up (d)	323 (197–489)	408 (167–547)	<.001
Sex: male	447 (62.3%)	905 (63.0%)	.77
Atrial fibrillation	425 (59.2%)	881 (61.4%)	.36
Coronary artery disease	262 (36.5%)	485 (33.8%)	.23
Diabetes mellitus	178 (24.8%)	335 (23.3%)	.49
Hyperlipidemia	475 (66.2%)	970 (67.5%)	.55
Hypertension	557 (77.6%)	1146 (79.8%)	.25
Tricuspid valve disease	150 (20.9%)	266 (18.5%)	.21
Peripheral vascular disease	91 (12.7%)	163 (11.4%)	.41

Values are presented as mean ± SD, as median (interquartile range), or as n (%).

Propensity score-matched analysis

- After applying 1:2 propensity score matching to the 9376 patients with TVPs from the unmatched analysis, the 718 patients with LCPs were matched with 1435 (15.3% of un- matched cohort) patients with TVPs with clinical characteristics as listed in Table 1.
- Fewer overall complications in the leadless group when compared with the propensity score–matched transvenous group (adjusted hazard ratio 0.44; 95% CI 0.32–0.60; P <.001).

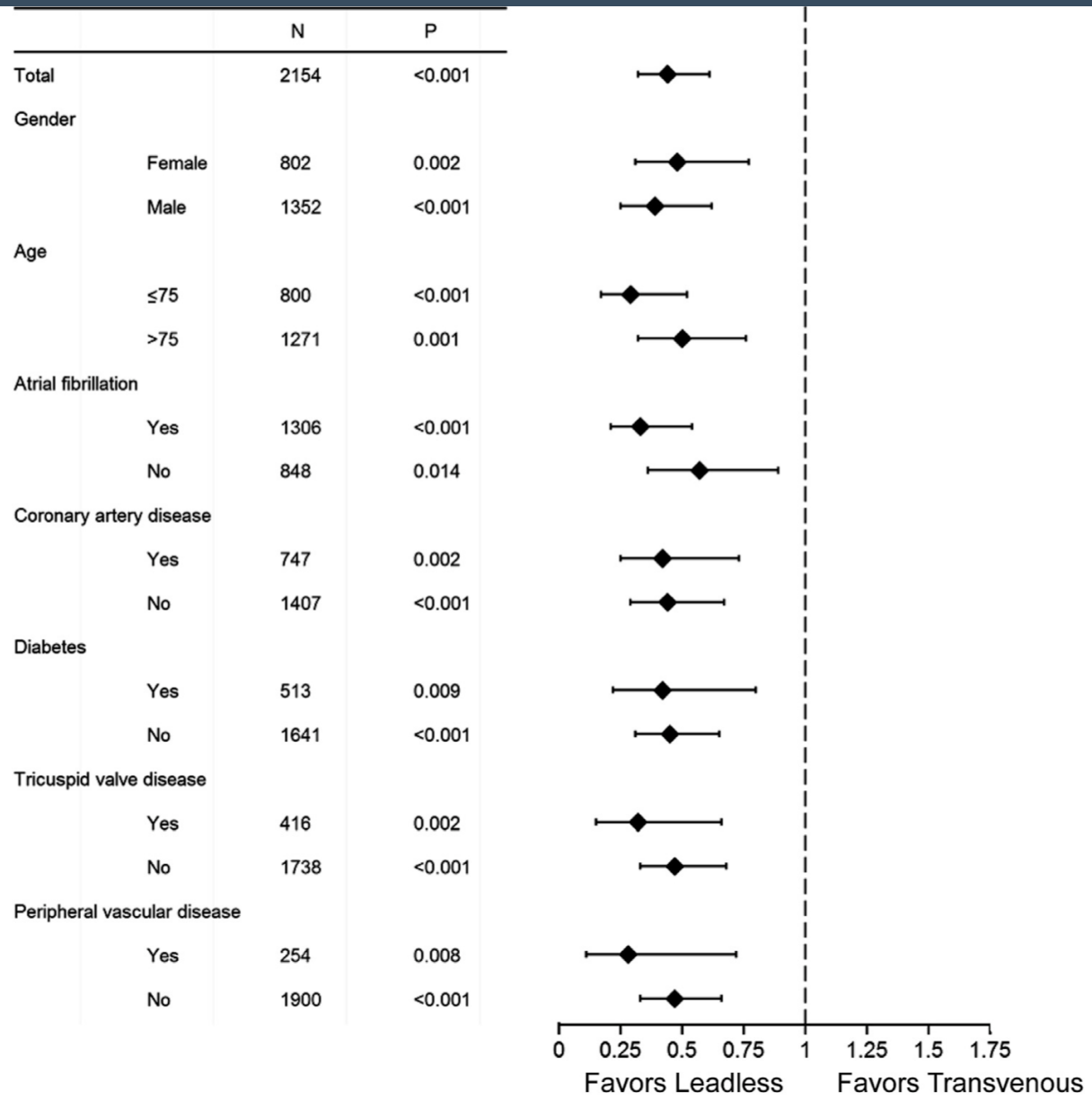


Figure 2 Plot presents adjusted hazard ratios and 95% confidence intervals for the risk of complication with the leadless pacemaker vs transvenous pacemaker in various patient subgroups.

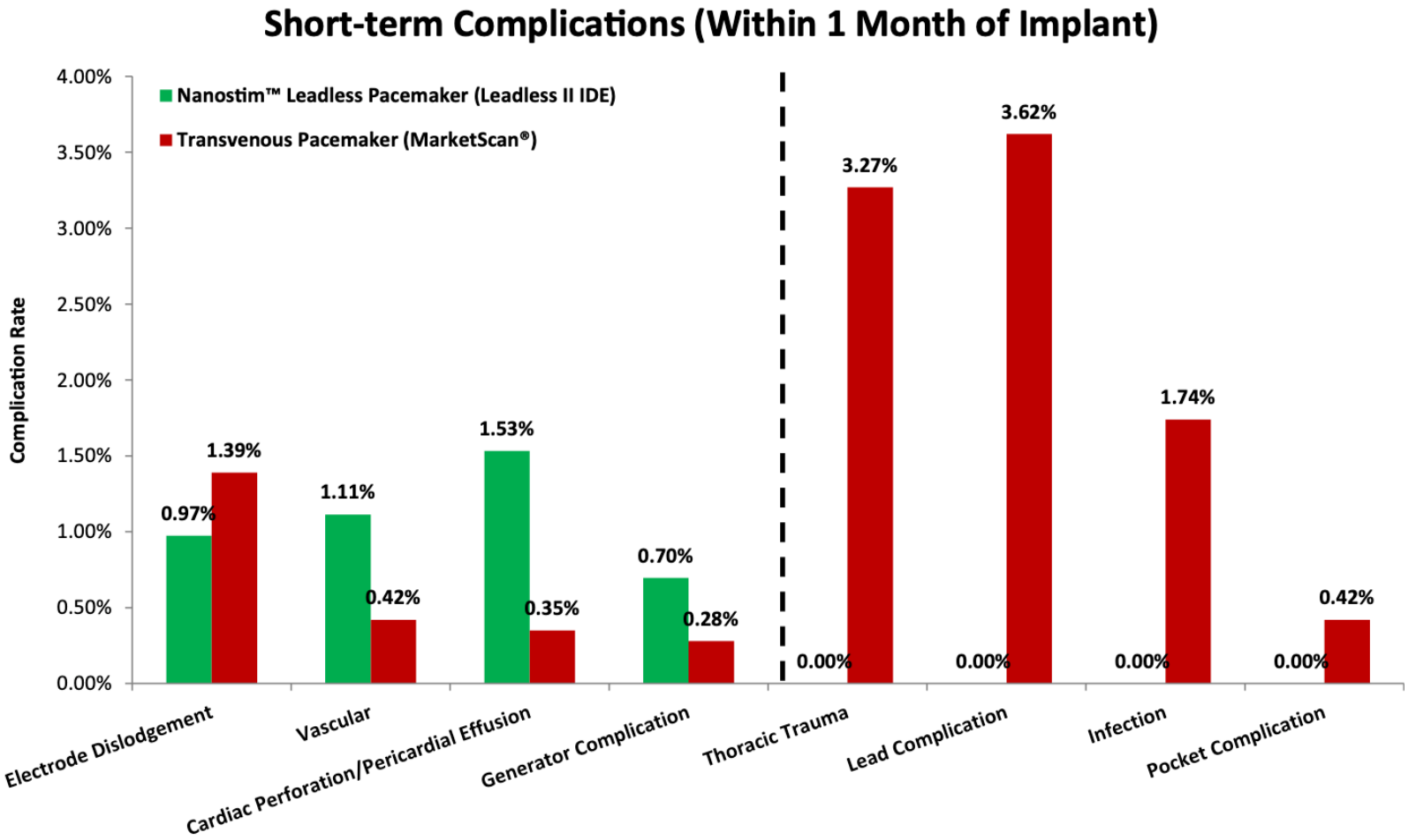


Figure 3 Short-term complication rates presented per category for patients with leadless pacemaker and patients with transvenous pacemaker. The exact rate is shown at the top of each bar.

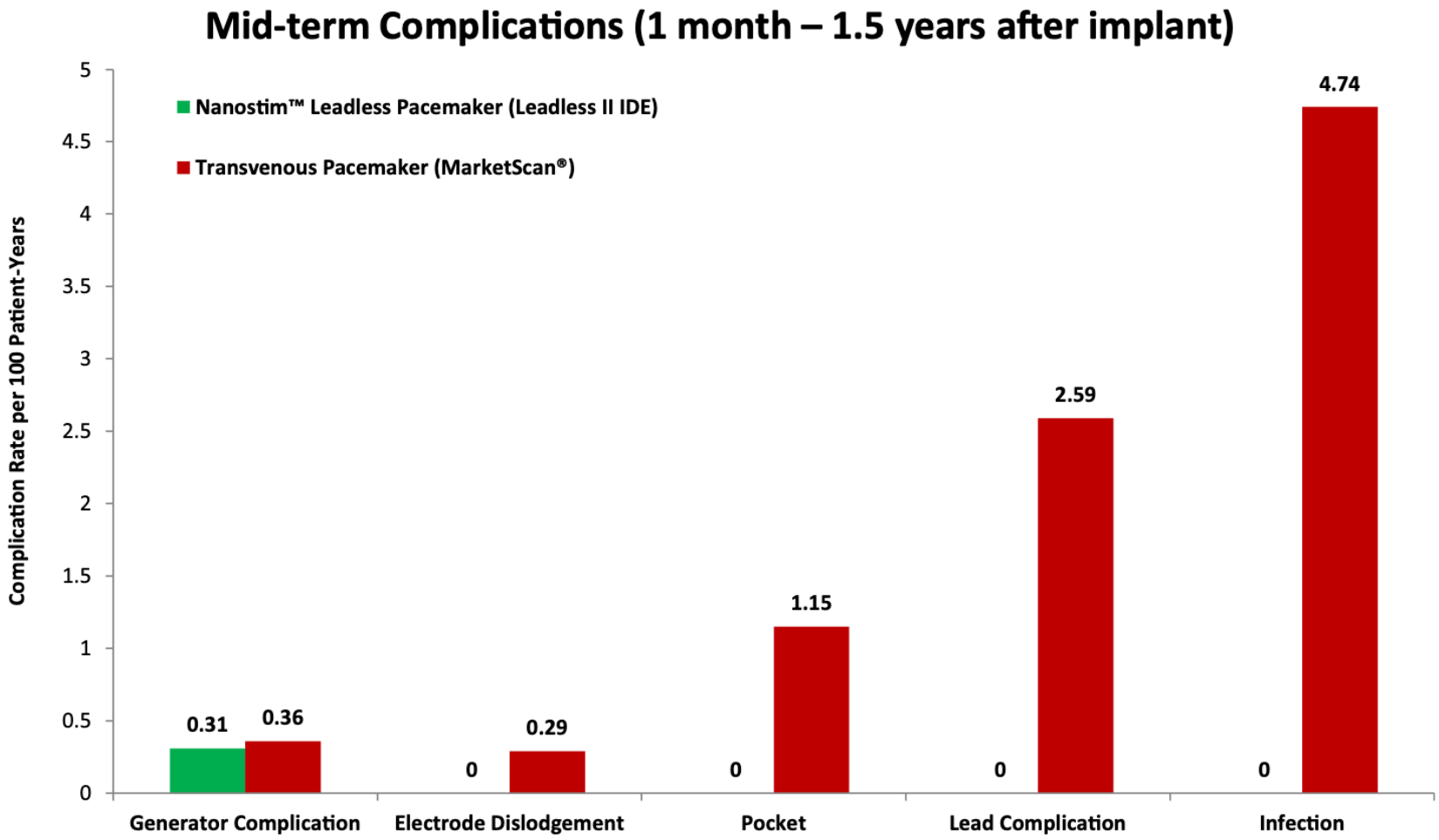


Figure 4 Mid-term complication rates presented per category for patients with leadless pacemaker and patients with transvenous pacemaker. The exact rate is shown at the top of each bar. One of the reported cardiac perforation complications also had an associated hemothorax as a result of a cardiopulmonary resuscitation performed during the procedure.

Discussion

- Overall reduction in both short- and mid-term events was driven by a virtual elimination of lead, pocket, and infectious complications from LCPs
- TVPs had slightly lower rates of uncommon but potentially serious complications of pericardial effusion and vascular events
- LCPs incurred serious cardiac tearing injuries that were reduced over time with operator experience and training (better outcomes when operators did more than 10 implants)

Limitations

- Full scope of long-term complications (including device extraction) from LCPs will not be understood for 10-15 more years.
- MarketScan databases are not a random sample but a large cohort from large employers
  - Underrepresented: self-insured and small/medium employers
  - Excluded: Medicare Advantage and traditional Medicare plans
- Repeat SAEs could have been accidentally treated as same instance = undercounting
- Single complications with encounters on nonconsecutive services dates = possible over counting

Limitations (cont.)

- Differing definitions of complications and types that can occur between the pacemaker groups
- LEADLESS II study SAEs adjudicated by independent committee, TVP SAEs not adjudicated
- LEADLESS II trial may have had more experienced operators, TVP operators could be from wider background of experience

Cleveland Clinic

Every life deserves world class care.

Comparative study of acute and mid-term complications with leadless and transvenous cardiac pacemakers

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OSIA 2nd Reader Presentation

PQHS 500

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Overview

- Study Objective
- Key Takeaways
- Limitations
- Future Studies

Study Objective

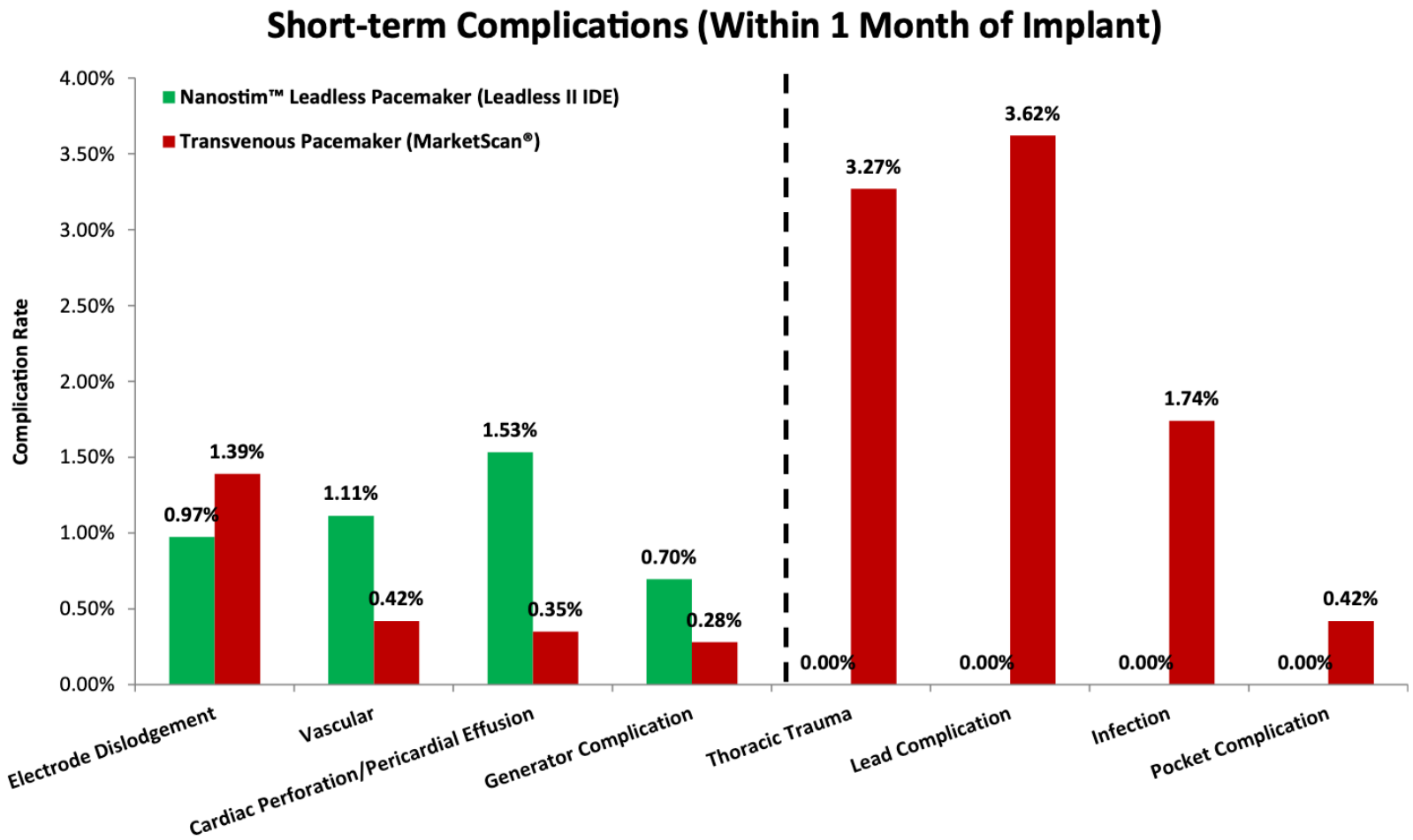
OBJECTIVE The purpose of this study was to compare complications between the LCP cohort from the LEADLESS Pacemaker IDE Study (Leadless II) trial and a propensity score–matched real-world TVP cohort.

Key Takeaways

- Patients with LCPs experienced fewer complications overall (hazard ratio 0.44; 95% confidence interval 0.32–0.60; P < .001)
- In both the short and mid term time frames, the LCP group had **no lead-related, pocket-related, and infectious complication**s. In the TVP group there were:
  - 2.59 lead-related complications per 100 patient-years (n = 36)
  - 0.29 electrode dislodgements per 100 patient years (n = 4)
  - 1.15 pocket complications per 100 patient years (n = 16)
  - 4.74 infections per 100 patient years (n = 66)

Key Takeaways

- Short term (<30 days):
  - Short-term complications were greatly reduced in the LCP cohort (5.8% vs 9.4%; P = 0.01)
  - However, there was a higher rate of pericardial effusions (1.53% vs 0.35%, P = .005) in the LCP group
  - There were similar rates of vascular events (1.11% vs 0.42%; P = .085), dislodgments (0.97% vs 1.39%; P = .54), and generator complications (0.70% vs 0.28%, P = 0.17)
  - LCPs had no thoracic trauma compared to patients with TVPs (rate of thoracic trauma 3.27%)



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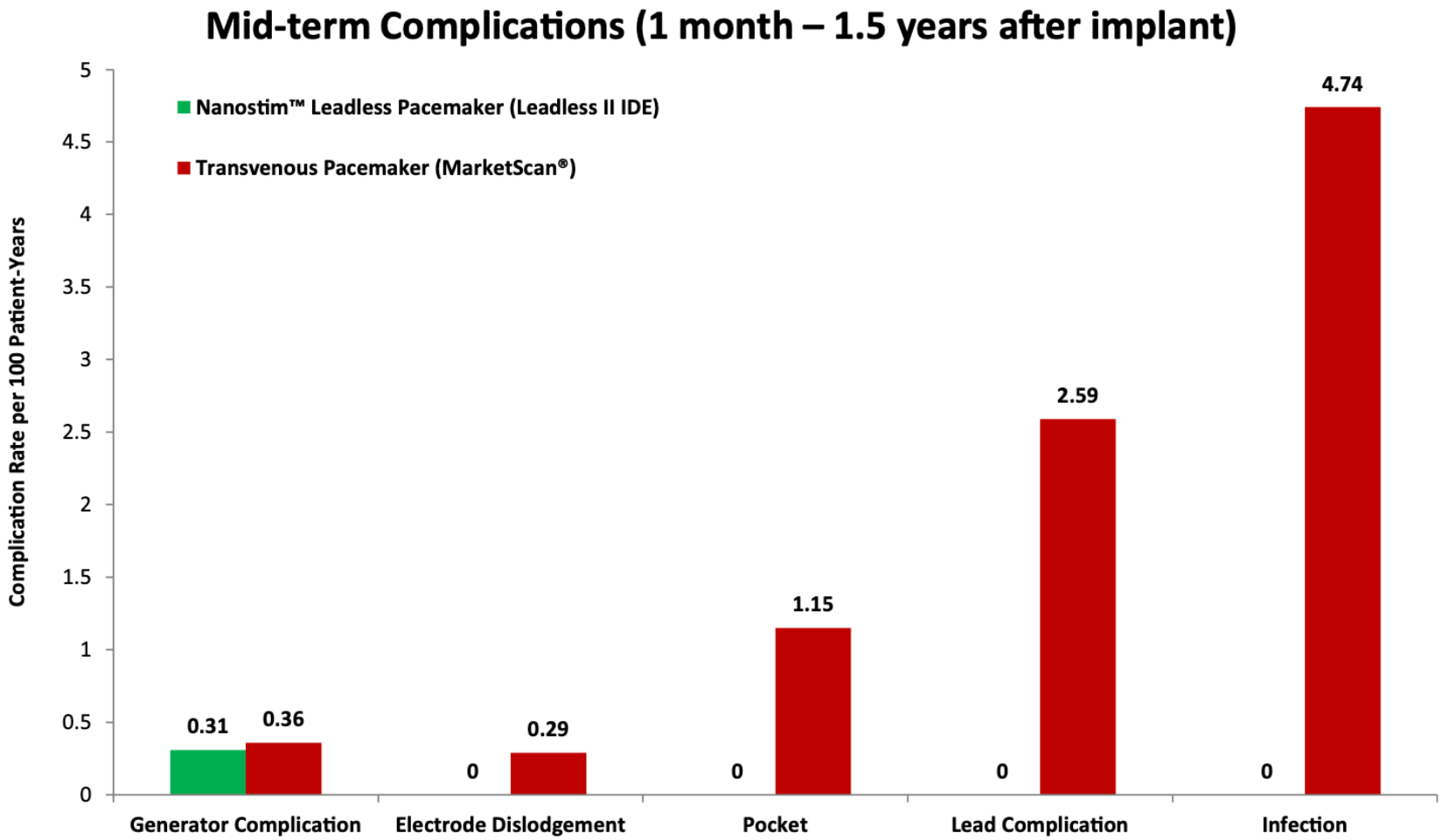

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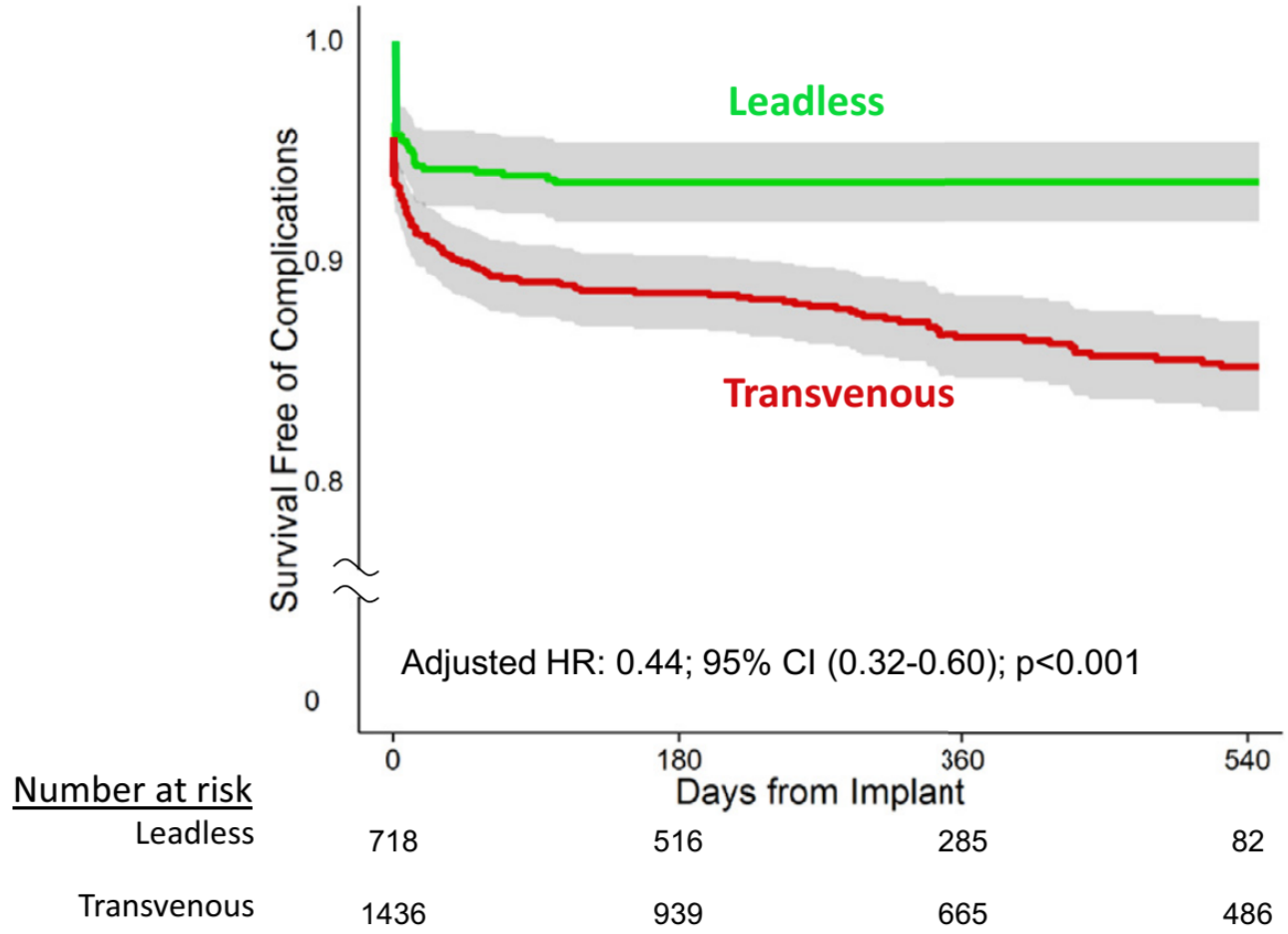

Figure 1 Kaplan-Meier curve (with 95% CI) illustrates that patients with LCPs were at a lower risk of experiencing a complication than were patients with TVPs. The Cox proportional hazards result is adjusted for age, sex, and baseline comorbidities. The starting point for the curves is the implantation of the device for both the LCP and TVP cohorts. CI = confidence interval; HR = hazard ratio; LCP = leadless pacemaker; TVP = transvenous pacemaker.

Propensity Score Matching

- 1:2 propensity score matching

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Limitations – Data Source Differences

- LCP data came from LEADLESS II clinical trial, which only included the Nanostim LCP device – is it unique?
- LEADLESS II trial had scheduled follow up at 2 weeks, 6 weeks, 3 months, and every 6 months
- Different levels of surgical experience in academic centers/research hospitals – lower complications because of more experience?
- TVP data originated from insurance claims database
  - Not a random sample of claims data – primarily drawn from large employers
  - Patients did not have scheduled follow up
- Can we compare these cohorts?

Limitations - Insurance Claims Data (TVP)

- Claims data is collected for billing
- Limited clinical data
  - Cannot identify complications requiring surgical management
  - No information on atrial fibrillation severity
  - No record of patient death
- Complications were identified by ICD codes
  - Did the researchers successfully identify all complications of interest?
  - Cannot definitively associate every complication with the TVP implant
  - Multiple diagnostic and procedure codes observed on the same or consecutive service dates were treated as a single occurrence, so repeat occurrences could be undercounted
  - Single complications with encounters on nonconsecutive service dates could be overcounted
  - There were complications in the LCPs group that could not have been quantified in patients with TVPs, including 5 instances of arrhythmia during implantation (0.70%), 2 acute migrations during implantation (0.28%), 1 angina event (0.14%), and 3 transient neurological events (0.42%).

Limitations – Device Differences

- Different types of complications occur with the different pacemaker systems
  - Different implantation technique/surgery types
  - “…the implantation technique involving a subcutaneous pulse generator and transvenous lead has remained unchanged and is the most common source of complications, occurring in up to 12% of device recipients.”
- Can we compare these devices?

Future Studies

- Longer follow-up duration
  - Complications were only evaluated for 18 months after implantation
  - Does not address long term complications such as battery depletion, lead fracture, incomplete capture, tricuspid valve regurgitation, infection, etc.
- Look at cohorts that were collected in a similar way
  - Possibly compare insurance claims data for LCPs vs TVP
  - This would produce cohorts with more comparable populations, follow up limitations, surgeon skill, etc.