Platelet Inhibition Post-CABG: Is it Time to aDAPT Management?

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Background/Rationale

- Cardiology guidelines strongly recommend DAPT ($P2Y_{12}$ inhibitor plus ASA) for 12 months in acute coronary syndrome (ACS) patients post coronary artery bypass graft (CABG)[1,2,3]
  - Based on lower quality evidence from CABG subgroup analyses of large trials[4,5,6]
- Survey found only 44.6% of Canadian cardiac surgeons routinely use DAPT in patients with ACS post-CABG[7]
- Beliefs regarding lack of benefit and increased bleed risk were the impetus behind prescribing choices[8]

Objectives

- **Primary:** does exposure to $P2Y_{12}$ inhibitor compared to no $P2Y_{12}$ inhibitor in ACS patients post-CABG:
  - Decrease risk of major adverse coronary event (MACE) in year post CABG
  - Increases risk of major bleeding in year post-CABG
- **Secondary**:
  - Compare individual MACE outcomes between $P2Y_{12}$ inhibitor versus no $P2Y_{12}$ inhibitor
  - Describe $P2Y_{12}$ inhibitor prescribing patterns over time

Outcomes:

- **Primary:** first occurrence of:
  - MACE in year post-CABG (all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization)
  - Major bleeding in year post-CABG (ED visit or hospital admission for intracranial, GI, GU, pulmonary, urologic or other bleed)
- **Secondary:**
  - Comparison of individual MACE components between groups
  - Description of $P2Y_{12}$ prescribing patterns over time

Methods: Design

- Retrospective cohort from Jan 1, 2010 to Dec 31, 2019
- Alberta Strategy for Patient Oriented Research Unit linkages across 5 databases:
- APPROACH registry: define cohort (ACS + CABG) and certain outcomes
- DAD and NACRS databases: other outcomes
- PIN: P2Y12 inhibitor and other prescription medication data
- AHS lab database

Methods: Inclusion and Exclusion

Inclusion Criteria

- Albertans ≥ 18 years of age.
- Admitted to hospital for ACS (STEMI, NSTEMI, unstable angina) & received CABG within 21 days (index event)

Exclusion Criteria

- Died during index event
- CABG in 2 years prior to index event
- Prescription fill for $P2Y_{12}$ inhibitor in 120 days prior to index event
- Prescription fill for anticoagulant in 120 days prior to index event or at time of discharge

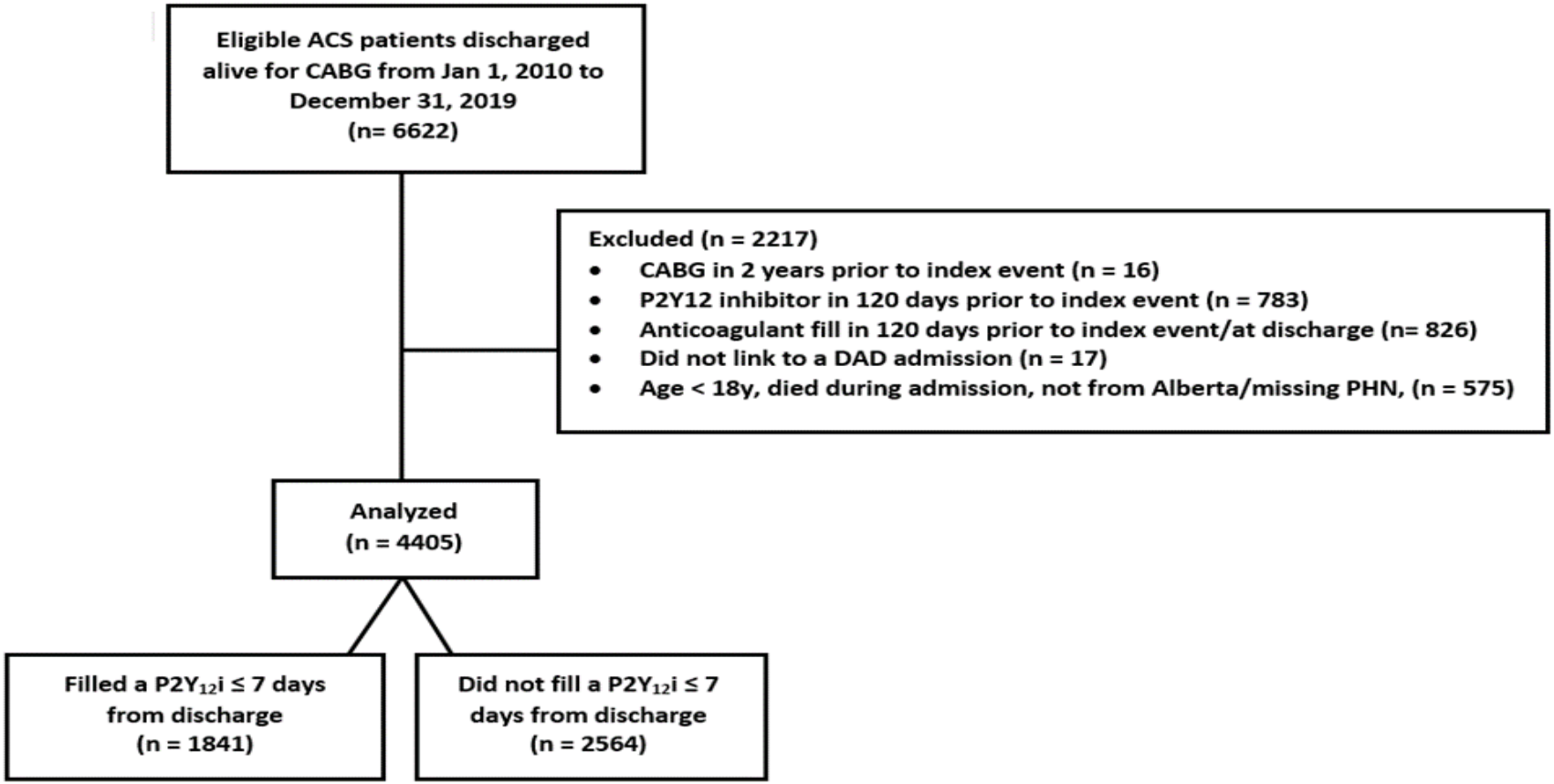
Methods: Exposure

- **$P2Y_{12}$ group:** filled $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, prasugrel) ≤ 7 days from discharge from index event
- **No $P2Y_{12}$ group:** did not fill $P2Y_{12}$ inhibitor ≤ 7 days from discharge from index event
- ASA 81 mg daily standard of care
  - All patients assumed to be receiving ASA during follow-up

Methods: Statistical Analysis

- Baseline characteristics:
  - Proportions for categorical: compared using $\chi 2$ test
  - Means with SD for continuous: compared using two sided t-test
- Time to event analysis performed using Cox proportional hazard models with HR and 95% CI
  - Covariate-adjusted model was constructed:
    - Age, BMI, sex, calendar year, DM, HF, HTN, smoking, prior PCI, number of grafts, STEMI, NSTEMI, UA, and concomitant medications filled within 90 days of D/C

Results: Cohort Characteristics



Results: Cohort Characteristics

- Patients in the $P2Y_{12}$ group:
  - Younger, male with fewer comorbidities
  - More concomitant cardioprotective medications
- $P2Y_{12}$ use:
  - Ticagrelor = 60.9%
  - Clopidogrel = 39.6%
- P2Y12 adherence = 61%; ; persistence = 70.1%

Adherence and Persistence Definitions

- Adherence:
  - Estimated using proportion of days covered (PDC)
  - PDC = (Sum of days covered in time frame) ÷ (number of days in time frame) × 100%, where number of days in time frame was 1 year post-index event discharge date
  - Patients with a proportion of days covered of ≥80% were classified as adherent
- Persistence:
  - Patients were persistent if they had gaps between P2Y12 inhibitor prescription fills of less than the days' supply plus a 15-day grace period

Results: Baseline Characteristics

	P2Y12 (n= 1841)	No P2Y12 (n=2564)	P-value
Comorbid Medical Conditions			
Prior myocardial infarction n (%)	449 (24.4)	876 (34.2)	<.0001
Prior stroke n (%)	54 (2.9)	105 (4.1)	.06
Prior TIA n (%)	40 (2.2)	75 (2.9)	.18
Prior CABG n (%)	379 (20.6)	897 (34.9)	<.0001
Prior PCI n (%)	326 (17.7)	423 (16.5)	.36
Smoking history			
Current n (%)	486 (26.4)	689 (26.9)	.004
Former n (%)	599 (32.5)	938 (36.6)	
Never/Missing n (%)	756 (41.1)	937 (36.5)	
Peripheral vascular disease n (%)	77 (4.2)	149 (5.8)	.02
Heart failure n (%)	130 (7.1)	260 (10.1)	.0003
Hypertension n (%)	1434 (77.9)	2101 (81.9)	.0006
Hyperlipidemia n (%)	1481 (80.5)	2252 (87.8)	<.0001
Diabetes n (%)	758 (41.2)	1038 (40.5)	.74
Liver Disease n (%)	28 (1.5)	38 (1.5)	.99
Chronic kidney Disease n (%)	134 (7.3)	220 (8.6)	.10
Peptic Ulcer Disease n (%)	44 (2.4)	51 (2.0)	.37

Results: Baseline Characteristics

P2Y12 inhibitor filled within ≤ 7 days of D/C	P2Y12 (n= 1841)	No P2Y12 (n=2564)	P-value
Clopidogrel n (%)	729 (39.6)	–	<.0001
Ticagrelor n (%)	1121 (60.9)	–	<.0001
Concomitant Medications		**n=2390***	
PPI n (%)	1546 (84.0)	1533 (64.1)	<.0001
Beta blockers n (%)	1784 (96.9)	2228 (93.2)	<.0001
RAASi n (%)	1549 (84.1)	1748 (73.1)	<.0001
MRA n (%)	147 (8.0)	182 (7.6)	.66
SGLT2i n (%)	163 (8.9)	91 (3.8)	<.0001
Statins n (%)	1801 (97.8)	2266 (94.8)	<.0001

Results: Primary Outcomes: MACE and Major Bleeding

First occurrence of composite of:

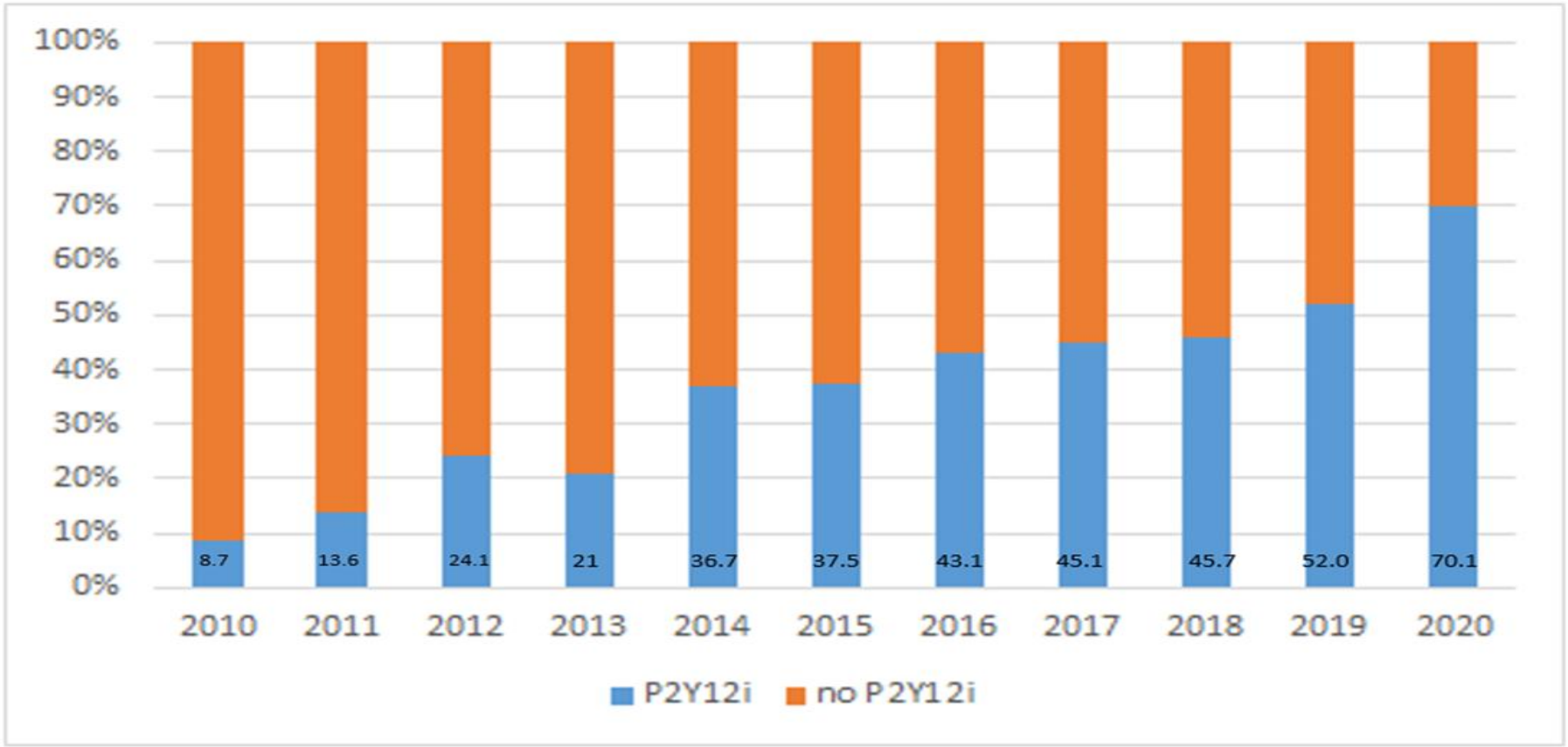
- MACE in year post-CABG (all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization)
- Major bleeding in year post-CABG (ED visit or hospital admission for intracranial, GI, GU, pulmonary, urologic or other bleed)

	$P2Y_{12}$ (n=1841)	No $P2Y_{12}$ (n=2564)	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
MACE, n (%)	334 (18.1)	524 (20.4)	0.91 (0.79, 1.04)	.18	0.93 (0.80, 1.08)	.35
Major bleeding, n (%)	135 (7.3)	157 (6.1)	1.20 (0.95, 1.51)	.12	1.26 (0.98, 1.62)	.07

Results: Secondary Outcome: Individual MACE

	$P2Y_{12}$ (n=1841)	No $P2Y_{12}$ (n=2564)	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Individual MACE outcomes:						
Death n (%)	26 (1.4)	80 (3.1)	0.46 (0.29, 0.73)	.001	0.64 (0.39, 1.05)	.077
Nonfatal Stroke n (%)	17 (0.9)	46 (1.8)	0.50 (0.29, 0.87)	.02	0.54 (0.30, 0.98)	.04
Nonfatal MI n (%)	146 (7.9)	95 (3.7)	2.19 (1.69, 2.83)	<.0001	1.53 (1.15, 2.04)	.004
Coronary revascularization n (%)	176 (9.6)	348 (13.6)	0.69 (0.57, 0.82)	<.0001	0.80 (0.66, 0.98)	.03

Results: Secondary Outcome: Temporal trends



Discussion: Composite MACE

- Results congruent with:
  - CURE[4] RCT: post-hoc analysis of ACS CABG subgroup:
    - DAPT did not decrease risk of MACE vs ASA
  - Verma et al (2019)[9]: MA 9 trials (2 RCT ACS post-CABG) comparing DAPT vs ASA -> no difference in MACE
- Sorensen et al (2011)[10]: observational trial of clopidogrel vs no clopidogrel in patients with MI post-CABG
  - Risk of death reduced in clopidogrel group
- 375 (14.6%) patients in no $P2Y_{12}$i group filled a $P2Y_{12}$i during the study period -> may have affected our finding of no difference
- $P2Y_{12}$ adherence = 61%; persistence = 70.1%

Discussion: Major Bleeding

- Major bleeding was not statistically different between groups (study not powered to detect difference)
  - Result consistent with major bleed results from prior studies:
    - CURE[4]
    - Meta-analysis by Zhao et al (2018)[11]
- Subpar medication adherence and persistence could also have contributed to this finding

Discussion: Individual MACE Outcomes

- $P2Y_{12}$ inhibitor group:
  - Reduced risk of nonfatal stroke and coronary revascularization and increased risk of nonfatal MI
  - Unexpected finding: would anticipate MI and coronary revascularization to trend together
  - May be due to residual confounding or competing risks
    - More patients alive during follow-up in $P2Y_{12}$i group to experience MI.

Limitations

1. Elimination of residual confounding not possible
   - Covariate adjusted Cox proportional hazards model
2. Some data and outcomes from administrative databases
   - APPROACH: define cohort and some outcomes
     - Prospective dataset: performs quality audits
3. Surrogate marker (prescription fill records) used to assess P2Y12i fills, adherence and persistence
   - May over- or underestimate true adherence and can miss medications (ASA)
   - Validated and consistent with previous studies[12,13]

Conclusion

- In this large population-based cohort study of ACS patients post-CABG:
  - $P2Y_{12}i$ was not associated with a lower risk of MACE compared to no $P2Y_{12}i$.
  - Major bleeding was not statistically different between groups (not powered)
- TACSI (Ticagrelor and ASA vs. ASA Only After Isolated Coronary Artery Bypass Grafting in Patients With Acute Coronary Syndrome) RCT[14]

Alberta Health Services

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