The BedMed Trials

Does the timing of blood pressure medication matter?

ALBERTA INNOVATES

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Pragmatic Trials Collaborative
Measuring What Matters

Faculty / Presenter Disclosure

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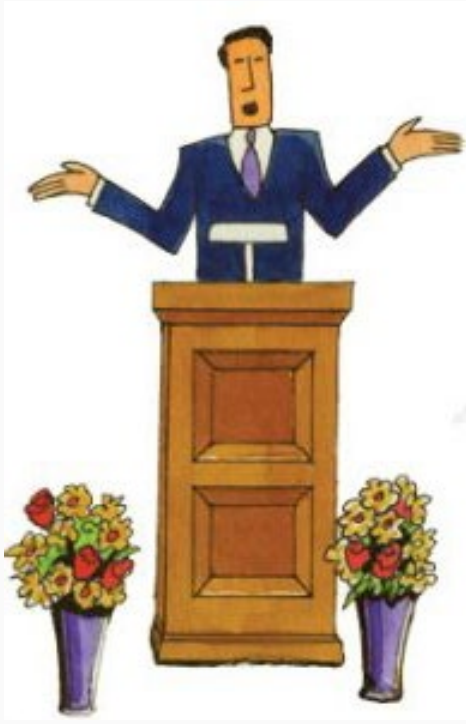
RELATIONSHIPS WITH FINANCIAL SPONSORS:

- Grants/Research Support: Ø
- Speakers Bureau/Honoraria: Ø
- Consulting Fees: Ø
- Other: Ø



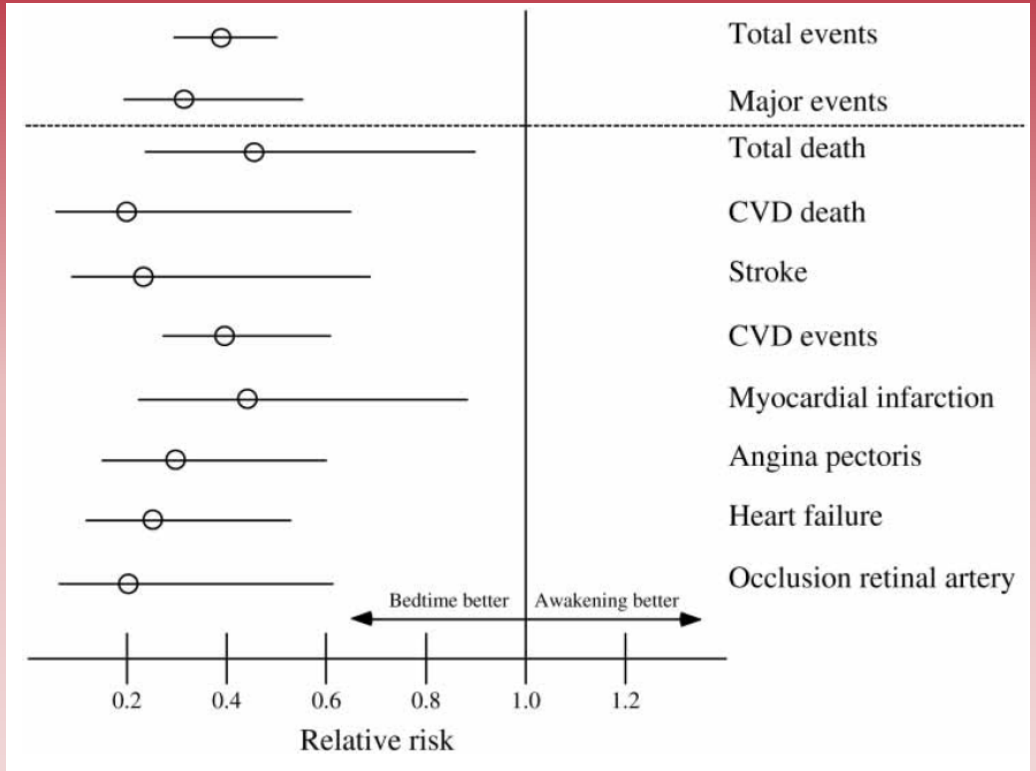
15 years

A Learning Healthcare System

MAPEC

- Hermida et al. (Spain) 2010
- N = 2156 hypertensive pts referred for ambulatory monitoring
- 56 yrs; 48% ♀; 20% Diabetes
- Intervention: ≥ 1 once-daily BP medication at bedtime vs all in AM
- Primary outcome = Major Adverse Cardiovascular Events (MACE)
- 5.6 years median follow-up, 255 primary outcome events

61% REDUCTION IN THE COMPOSITE MACE PRIMARY OUTCOME!!



Chronobiol Int. 2010 Sep;27(8):1629-51

MAPEC

General Reasons for Scepticism:

- Too good to be true?
- Why Chronobiology International?

Nerdy Reasons for Scepticism:

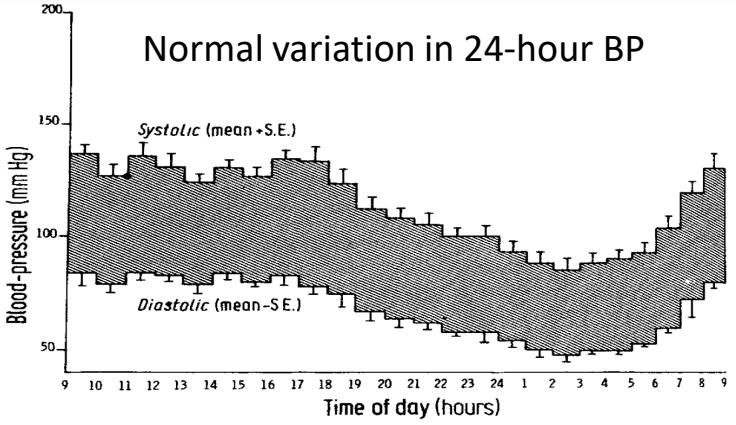
- 8 different trials point to the same trial registry.
- Allocation not concealed
- Incomplete reporting on dropouts, loss-to-follow-up, and how they were handled.

Chronobiol Int. 2010 Sep;27(8):1629-51

Does switching blood pressure medication to bedtime lower cardiovascular risk?

Rationale:

- Overnight BP is a better predictor of cardiovascular events than is daytime BP
- Bedtime BP medication might preferentially lower overnight BP



Lancet. 1978 Apr 15;1(8068):795-7.

Lancet. Jun 17 2023;401(10393):2041-2050; N Engl J Med 2003;348(24):2407-2415; Hypertension 2008;51(1):55-61

The big ask …

The clear answer…

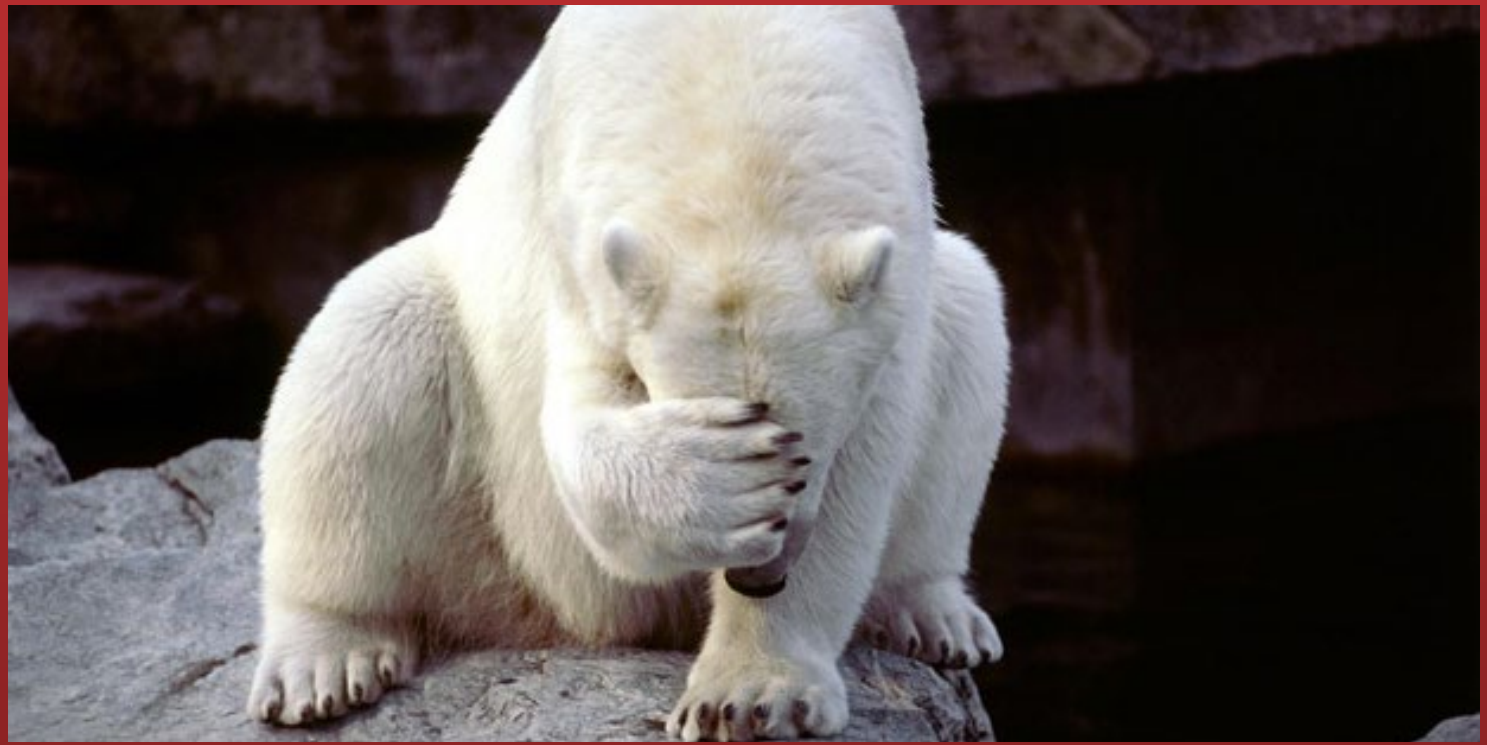
The Pragmatic Trials Collaborative

Measuring What Matters

Physicians engaged

What about Data?

Beware the unexpected...



Alberta

Freedom To Create. Spirit To Achieve.

Data partner?

SPOR Data!!

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What we did …

Two separate RCTs

- Frail/complex older adults are underrepresented in typical RCTs
- Benefits/risks could be meaningfully different

BedMed

BedMed - Frail

BedMed (in a nutshell)

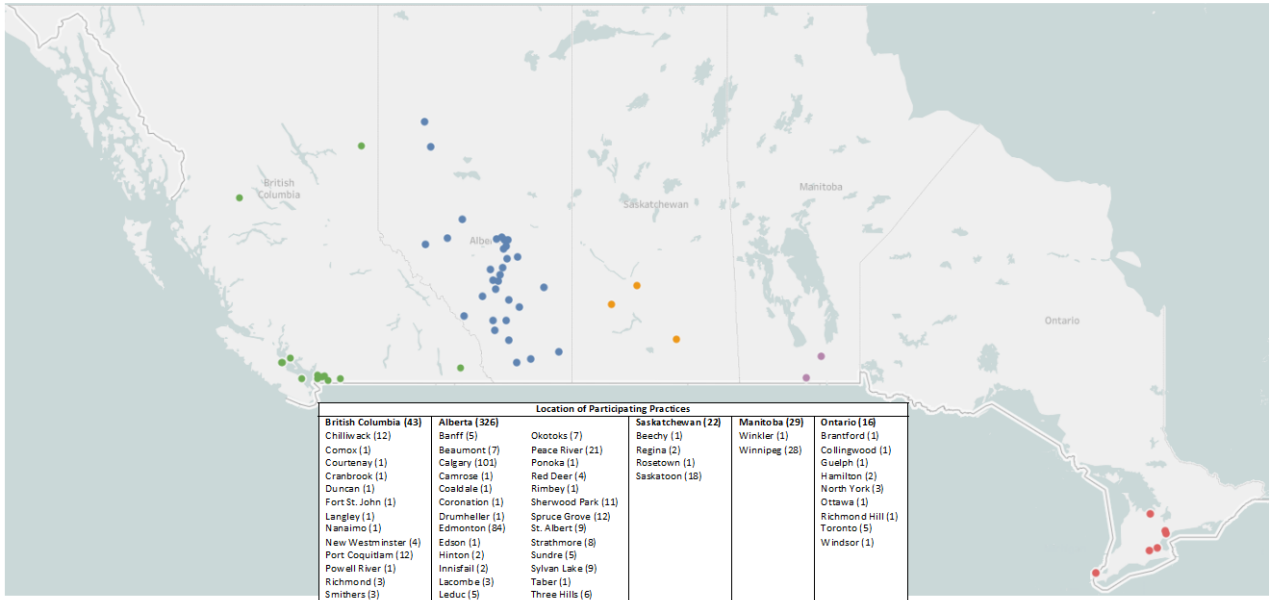
Design

- Open 1:1 parallel PROBE design (prospective randomized open blinded-endpoint assessment)
- Recruited March 2017 to May 2022, followed until Dec 2023

BedMed Protocol / Analytic Plan: BMJ Open. 2022 Feb 24;12(2):e059711

Setting

- Recruited in 5 Canadian provinces (BC, AB, SK, MB, ON)
- **436 primary care providers** (PCPs) in **61 different cities** mailed recruitment packages to all their hypertensive patients
- **Administrative health data linkages for 92.6%** of participants (residents of British Columbia, Alberta, and Manitoba) – including reasons for hospitalization /ED visits & community physician diagnoses



Location of Participating Practices

British Columbia (43)	Alberta (326)		Saskatchewan (22)	Manitoba (29)	Ontario (16)
Chilliwack (12)	Banff (5)	Okotoks (7)	Beechy (1)	Winkler (1)	Brantford (1)
Comox (1)	Beaumont (7)	Peace River (21)	Regina (2)	Winnipeg (28)	Collingwood (1)
Courtenay (1)	Calgary (101)	Ponoka (1)	Rosetown (1)		Guelph (1)
Cranbrook (1)	Camrose (1)	Red Deer (4)	Saskatoon (18)		Hamilton (2)
Duncan (1)	Coaldale (1)	Rimbey (1)			North York (3)
Fort St. John (1)	Coronation (1)	Sherwood Park (11)			Ottawa (1)
Langley (1)	Drumheller (1)	Spruce Grove (12)			Richmond Hill (1)
Nanaimo (1)	Edmonton (84)	St. Albert (9)			Toronto (5)
New Westminster (4)	Edson (1)	Strathmore (8)			Windsor (1)
Port Coquitlam (12)	Hinton (2)	Sundre (5)			
Powell River (1)	Innisfail (2)	Sylvan Lake (9)			
Richmond (3)	Lacombe (3)	Taber (1)			
Smithers (3)	Leduc (5)	Three Hills (6)			
Vancouver (2)	Lethbridge (9)	Vulcan (2)			
	Manning (2)	Wetaskiwin (1)			
	Medicine Hat (1)	Whitecourt (2)			


Robyn
Ping
David
Darryl
Farah
Scott
Marian

Participants

Inclusion Criteria

- Hypertension Dx
- ≥1 once-daily BP medication
- Community-dwelling
- ≥19 years of age

Exclusion Criteria

- **Glaucoma** Dx, or glaucoma Rx
- Sleep disrupting **shift work** (> 3 shifts per month during regular sleep hours)
- Considered palliative or unable to consent by primary care provider

Baseline Characteristics	Bedtime N = 1677	Morning N = 1680
Age – years, median (IQR)	67 (60, 73)	67 (61, 73)
Female – no. (%)	950 (56.6)	943 (56.1)
White – no. (%)	1565 (93.3)	1587 (94.5)
Comorbidities – no. (%)		
Sleep apnea	377 (22.5)	341 (20.3)
Diabetes	289 (17.2)	311 (18.5)
CAD	172 (10.3)	188 (11.2)
CKD	119 (7.1)	129 (7.7)
Stroke	75 (4.5)	75 (4.5)
CHF	28 (1.7)	32 (1.9)
Number of BP meds – no. (%)		
1	895 (53.4)	908 (54.0)
2	588 (35.1)	577 (34.3)
3	155 (9.2)	170 (10.1)
≥4	39 (2.3)	25 (1.5)
BP medications – no. (%)		
ACEI	584 (34.8)	631 (37.6)
ARB	536 (32.0)	471 (28.0)
CCB	479 (28.2)	489 (29.1)
Diuretic	446 (26.6)	472 (28.1)
Combination pill	315 (18.8)	300 (17.9)
Beta-blocker	289 (17.2)	278 (16.5)
Other	26 (1.6)	21 (1.3)

Intervention

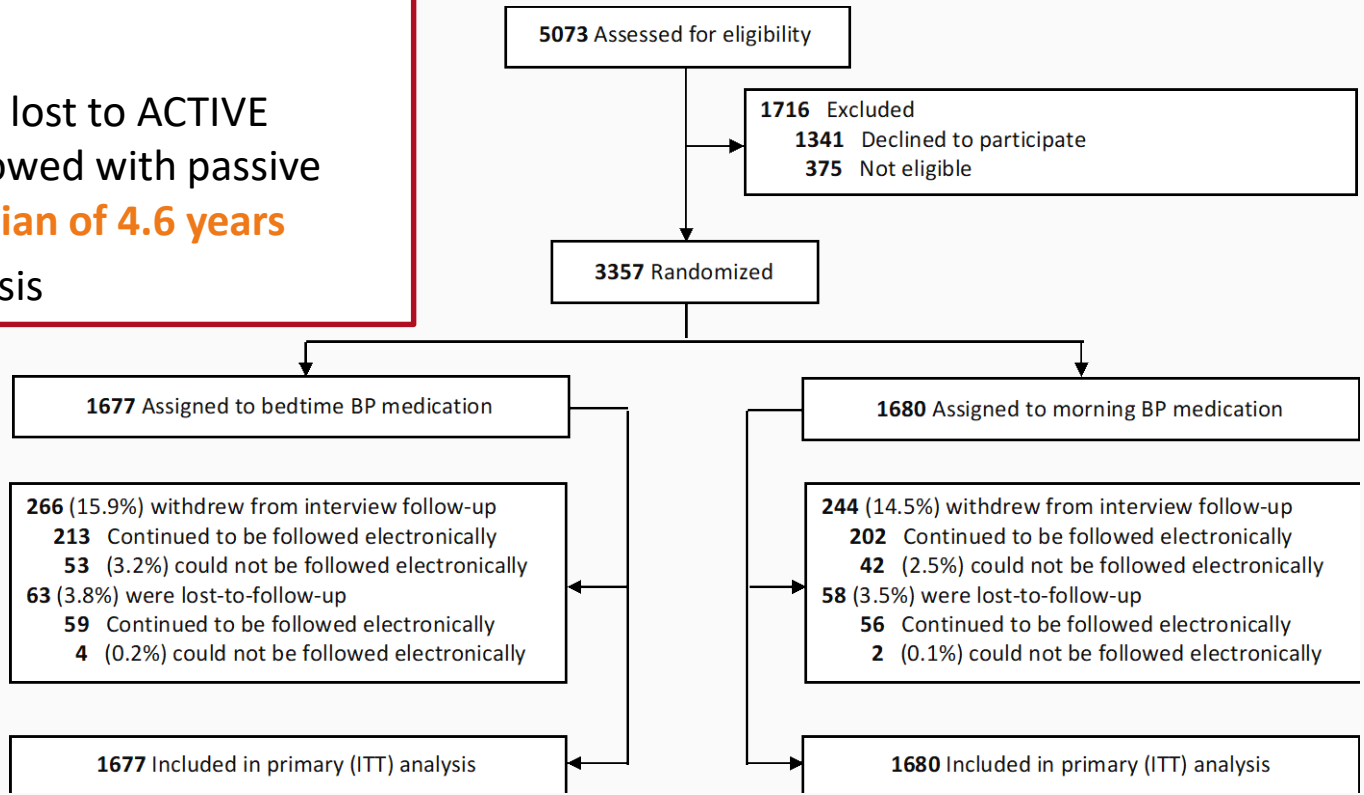
- **INTERVENTION: Taking all once-daily BP medication when getting ready for bed** (if intolerant of bedtime use, asked to take it with dinner, rather than switching back to morning)
- **CONTROL: Taking all once-daily BP medication upon waking in AM**
- Allocation obtained while dialoging **directly** with a research assistant who was simultaneously accessing the **central** REDCap server's randomization module (random blocks of 10 or 12, stratified by province) *ensuring **irreversible and concealed allocation***
- Follow-up at 1-week, 6-weeks, 6-months and every 6-months thereafter via telephone or e-mail survey
- **Blinded adjudication committee** examined administrative health data + pt reports and sought information from family physicians when discrepancies were present or events were reported from only one source

Outcomes

- **Primary:** All-cause death or hospitalization/emergency department (ED) visit for stroke, acute coronary syndrome, or heart failure
- **Secondary efficacy**
  - Each component of primary outcome
  - All cause unplanned hospitalization/ED visit
- **Secondary Safety**
  - **Postural hypotension-related:** Non-vertebral fracture, hip fracture, falling, syncope, lightheadedness
  - **Vision-related:** New glaucoma diagnosis, self-reported worsening of vision
  - **Cognition-related:** Cognitive decline at 18-months, new impairment consistent with dementia, nursing home admission

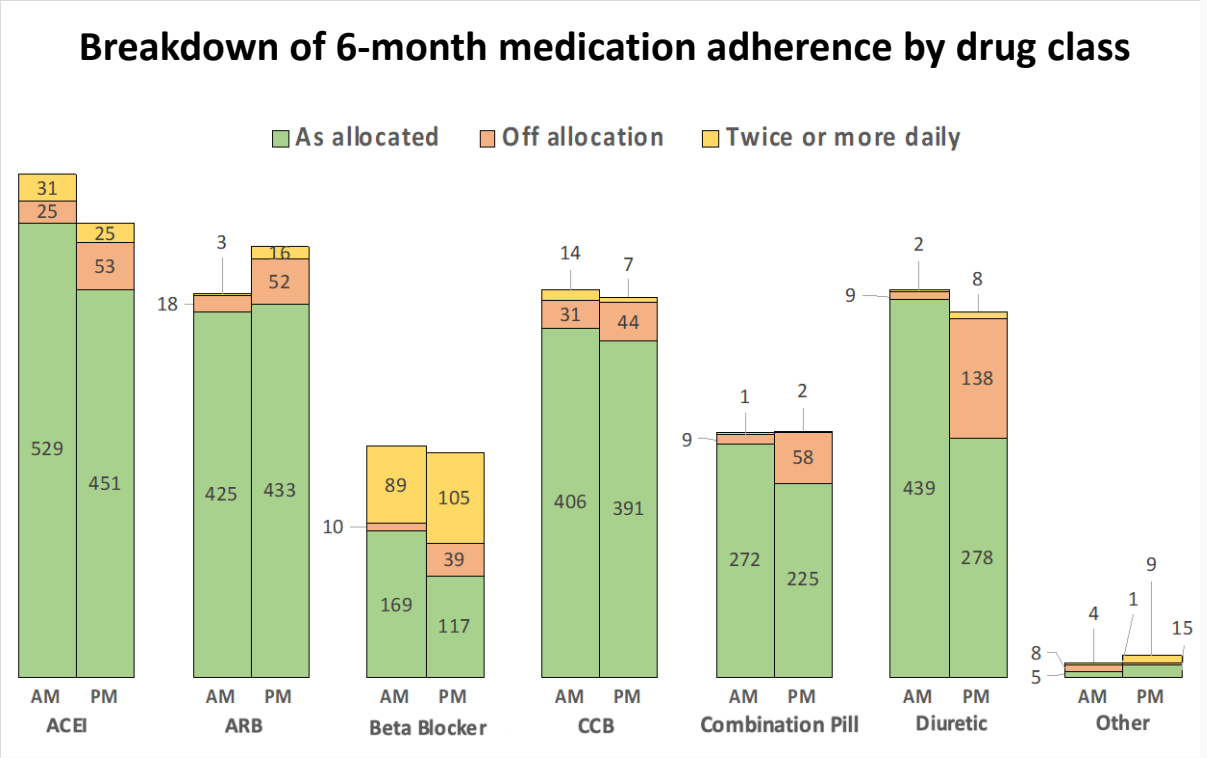
Patient Flow

- **3% withdrew or were lost to all follow-up**
  - Bedtime 57/1677 (3.4%)
  - Morning 44/1680 (2.6%)
- An additional 16% were lost to ACTIVE follow-up but were followed with passive surveillance over a **median of 4.6 years**
- Intention-to-treat analysis

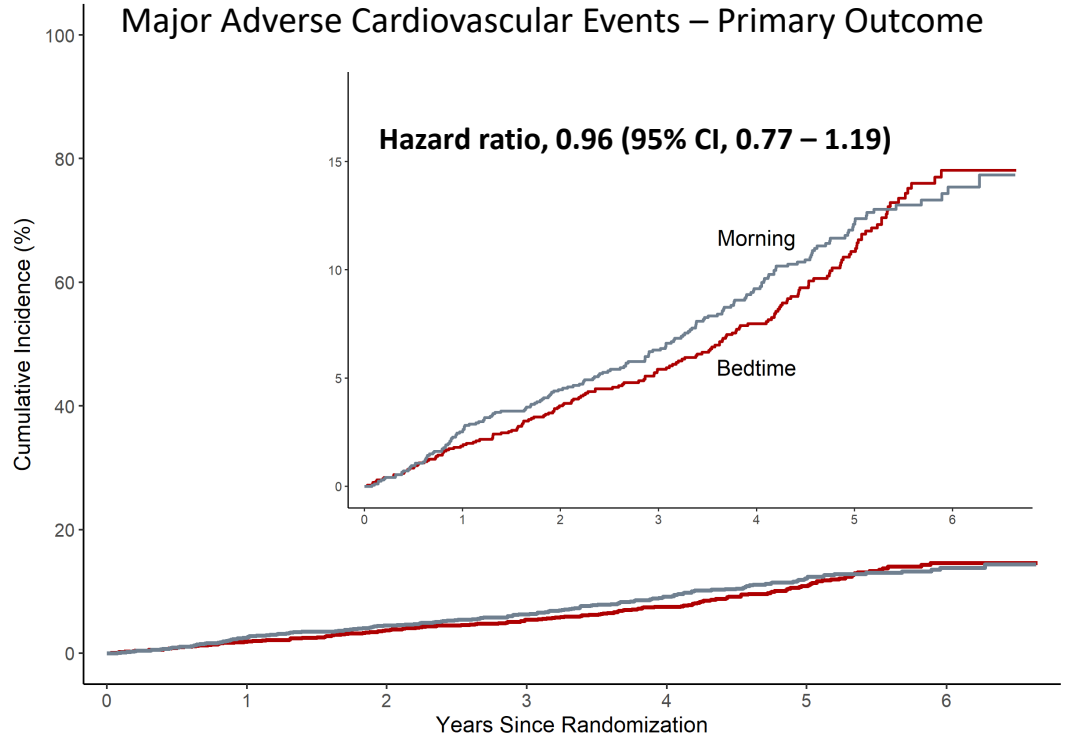


Adherence to allocation

- **At 6-months**
  - **83% of once daily BP Rx were per allocation in the bedtime group vs 95% in morning**
  - ≥1 once-daily BP Rx was per allocation for 88% of bedtime and 97% of morning participants. This gradually fell over time, with the lowest adherence being 70% vs 88% at 6-years

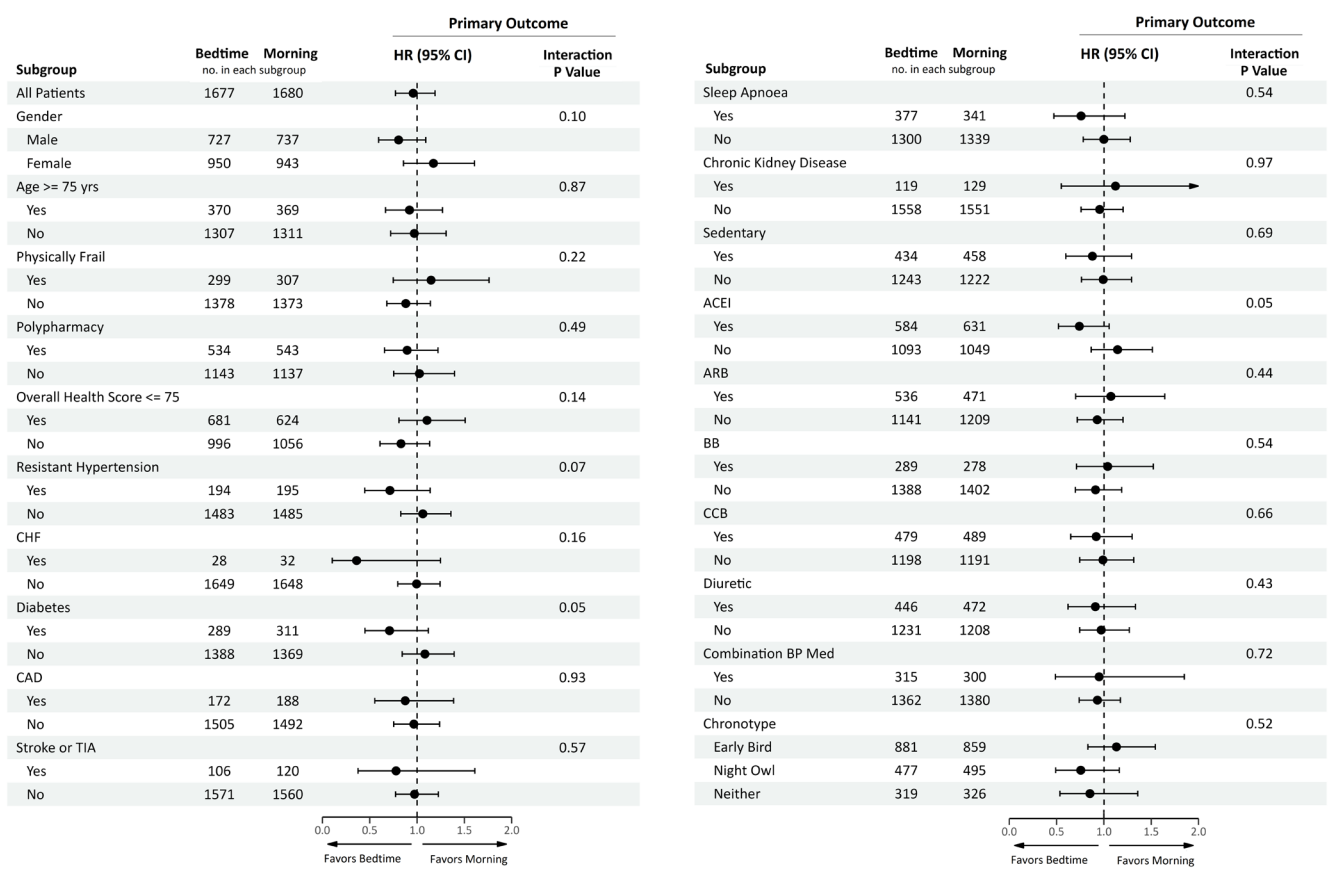


Primary Outcome



Bedtime N = 1677		Morning N = 1680		P Value
N (%)	Rate/100 patient-yr	N (%)	Rate/100 patient-yr	
163 (9.7)	2.30	173 (10.3)	2.44	0.70

Primary Outcome - Subgroups



Secondary Outcomes

- **No difference in ANY outcome** including primary outcome components, all-cause unplanned hospitalization/ED visits, and safety outcomes looking for postural hypotension-related, vision-related, and cognition-related adverse effects

Outcome	Bedtime N = 1677		Morning N = 1680		HR/RR (95% CI)	P Value
	n (%)	Rate/100 patient-yr	n (%)	Rate/100 patient-yr		
Secondary – Efficacy						
Primary Outcome Components						
All-cause mortality	81 (4.8)	1.11	94 (5.6)	1.28	0.90 (0.67 - 1.22)	0.50
Hosp/ED for stroke	27 (1.6)	0.37	32 (1.9)	0.44	0.86 (0.52 - 1.44)	0.57
Hosp/ED for ACS	48 (2.9)	0.67	39 (2.3)	0.54	1.25 (0.82 - 1.91)	0.30
Hosp/ED for CHF	30 (1.8)	0.41	43 (2.6)	0.59	0.72 (0.45 - 1.15)	0.17
All-cause unplanned hospitalization/ED visit	993 (59.2)	23.26	1047 (62.3)	25.15	0.93 (0.85 - 1.02)	0.10
Secondary – Safety						
Postural Hypotension Related						
Non-vertebral fracture	152 (9.1)	2.18	166 (9.9)	2.40	0.92 (0.74 - 1.14)	0.44
Hip fracture	20 (1.2)	0.27	31 (1.8)	0.43	0.65 (0.37 - 1.15)	0.14
Falling	4.9 (11.7)	-	5.0 (11.2)	-	0.96 (0.86 - 1.07)	0.47
Syncope	0.6 (3.8)	-	0.6 (4.1)	-	1.28 (0.93 - 1.75)	0.12
Light-headedness	18.8 (25.2)	-	20.3 (26.2)	-	0.95 (0.90 - 1.00)	0.06
Vision related						
New glaucoma diagnosis	43 (2.6)	0.60	39 (2.3)	0.54	1.13 (0.73 - 1.74)	0.58
Worsening of vision	420 (25.0)	-	411 (24.5)	-	1.02 (0.89 - 1.17)	0.74
Cognition related						
18-month cognitive decline	376 (26.0)	-	395 (26.5)	-	0.98 (0.85 - 1.13)	0.82
New dementia diagnosis	89 (5.3)	-	83 (4.9)	-	1.12 (0.83 - 1.51)	0.48
Nursing home admission	38 (2.3)	0.52	26 (1.5)	0.36	1.38 (0.83 - 2.27)	0.21

BedMed - Frail (in a nutshell)

Methods

BedMed - Frail

- **Design:** Open, 1:1 RCT with **opt-out consenting**
- **Setting:** **17 Continuing Care Wards** in Alberta; **Administrative health data linkage** + **clinical nursing data** (RAI-MDS 2.0)
- **Inclusion:** ≥2 Dx hypertension (2002 onwards); ≥1 once-daily BP Rx
- **Exclusion:** Glaucoma Dx or Tx; Opted out
- **Intervention:** Use of all once-daily BP Rx at **bedtime**
- **Control:** **No change** in BP Rx timing (largely morning use by default)
- **Randomization:** Simple, central, via provincial data analyst who communicates allocation directly to facility pharmacist

BedMed-Frail Protocol / Analytic Plan: BMJ Open. 2023 Aug 1;13(8):e074777

Outcomes

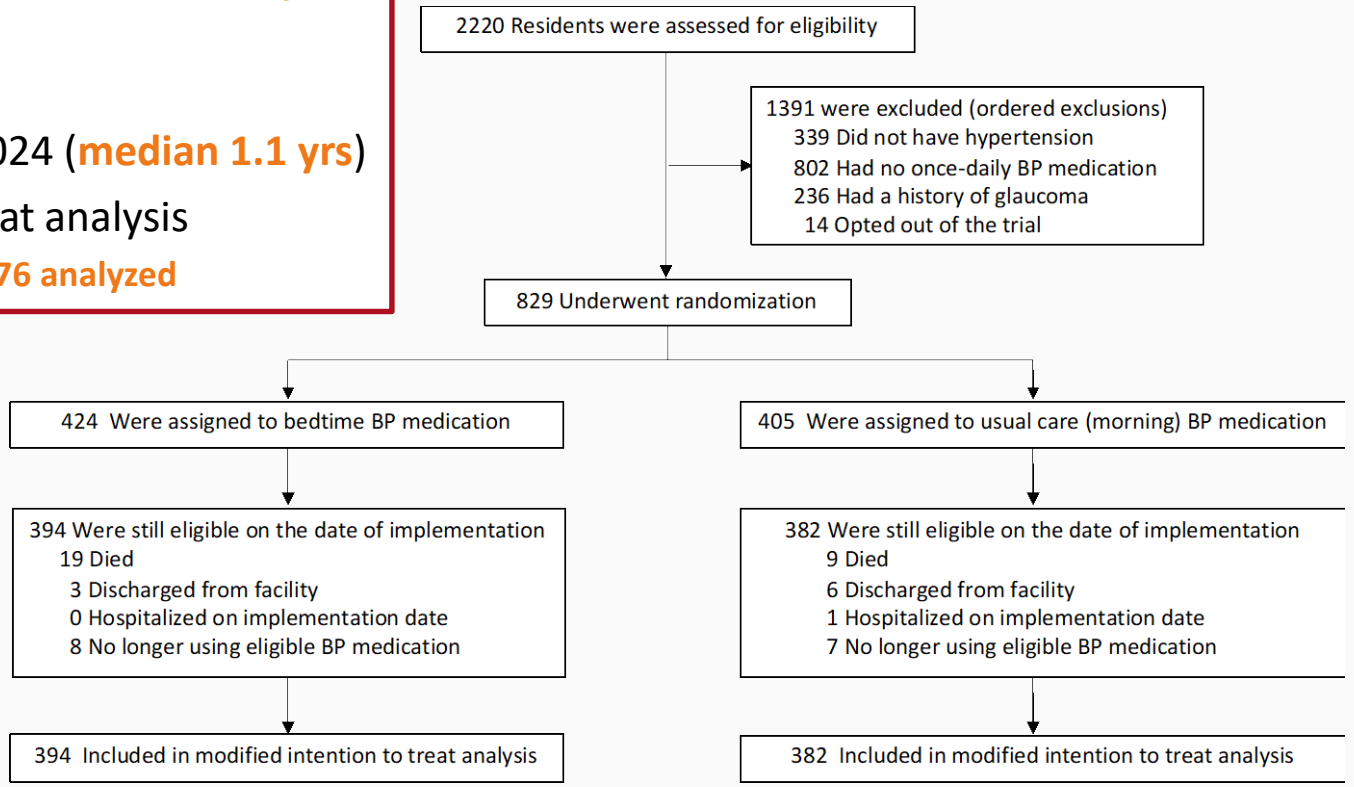
BedMed - Frail

- **Primary:** All-cause death or hospitalization/emergency department (ED) visit for stroke, MI/ACS, or CHF = “MACE”
- **Secondary efficacy**
  - Each component of primary outcome
  - All-cause unplanned hospitalization/ED visit
- **Secondary Safety**
  - **Falls/Fractures:** **Non-vertebral fracture**, **fall in the last 30 days**
  - **Cognitive/Behavioral:** **Deteriorated cognition**, **problem behaviors**, use of antipsychotic medication or physical restraints, indicators of depression or anxiety, use of anti-anxiety medication, use of sleeping pill
  - **Other:** Partial or full thickness **skin ulceration** (stage 2-3), urinary incontinence

Participant Flow

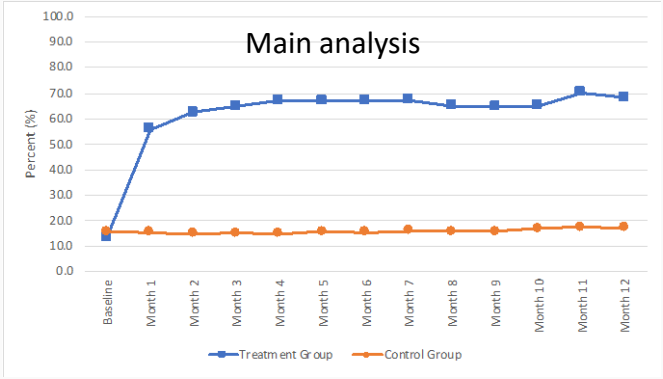
BedMed - Frail

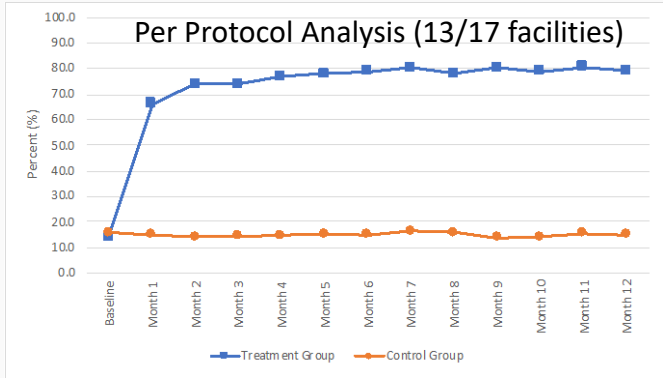
- Only 14/843 **(1.7%) eligible pts opted out**
- **4% withdrew or were lost to all follow-up**
  - Bedtime 14/394 (**3.6%**)
  - Morning 18/382 (**4.7%**)
- May 25 2020 → Feb 29 2024 (**median 1.1 yrs**)
- **Modified** intention-to-treat analysis
  - N = 829 randomized; **N = 776 analyzed**



Participants and Adherence

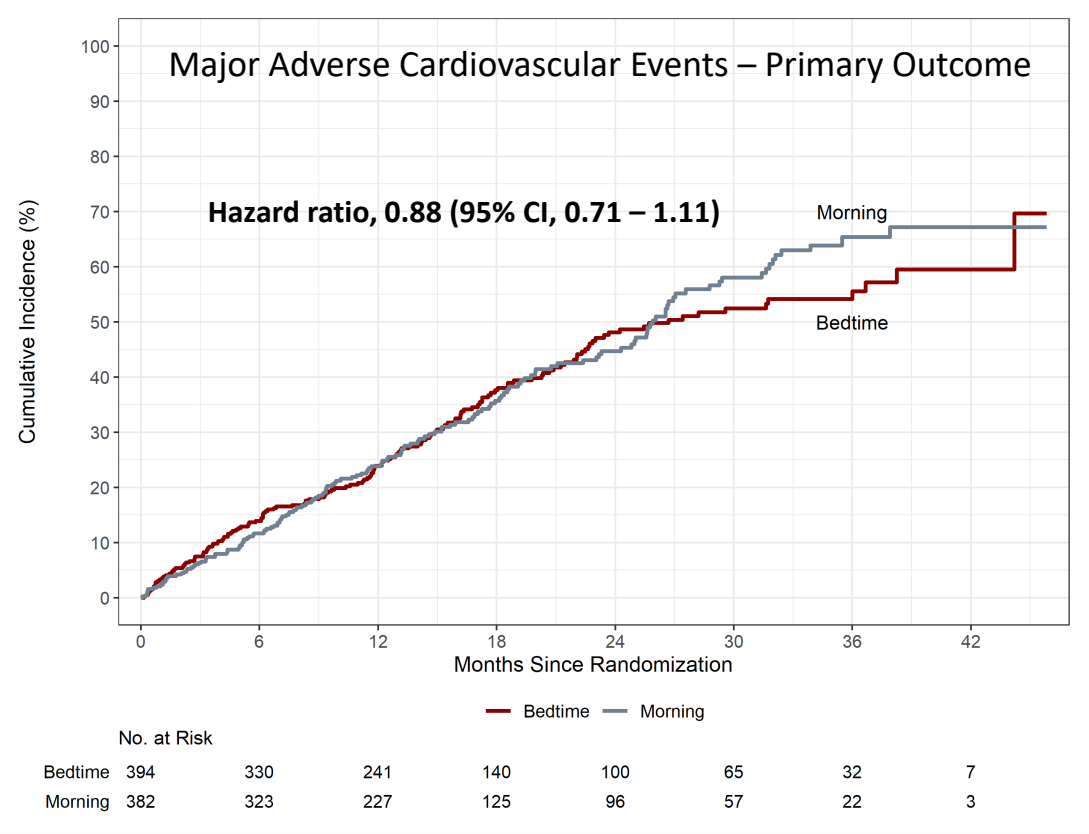
Mean % of antihypertensive doses at bedtime





Baseline Characteristic	Bedtime N = 394	Morning N = 382
Age – years, median (IQR)	88 (80, 92)	88 (81, 92)
Female – no. (%)	289 (73.4)	273 (71.5)
Comorbidities – no. (%)		
Dementia	338 (85.8)	326 (85.3)
CKD	190 (48.2)	187 (49.0)
Diabetes	196 (49.7)	171 (44.8)
CAD	168 (42.6)	139 (36.4)
CHF	139 (35.3)	118 (30.9)
Stroke	119 (30.2)	105 (27.5)
Sleep Apnea	96 (24.4)	94 (24.6)
Number of BP meds – no. (%)		
1	235 (59.6)	231 (60.5)
2	124 (31.5)	124 (32.5)
≥ 3	35 (8.9)	27 (7.1)
BP medications – no. (%)		
CCB	169 (42.9)	180 (47.1)
ACEI	145 (36.8)	148 (38.7)
ARB	116 (29.4)	101 (26.4)
Beta blocker	87 (22.1)	69 (18.1)
Diuretic	73 (18.5)	63 (16.5)
Other	2 (0.5)	4 (1.0)

Primary Outcome



Bedtime N = 394		Morning N = 382		P Value
N (%)	Rate/100 patient-yr	N (%)	Rate/100 patient-yr	
160 (40.6)	29.4	160 (41.9)	31.5	0.28

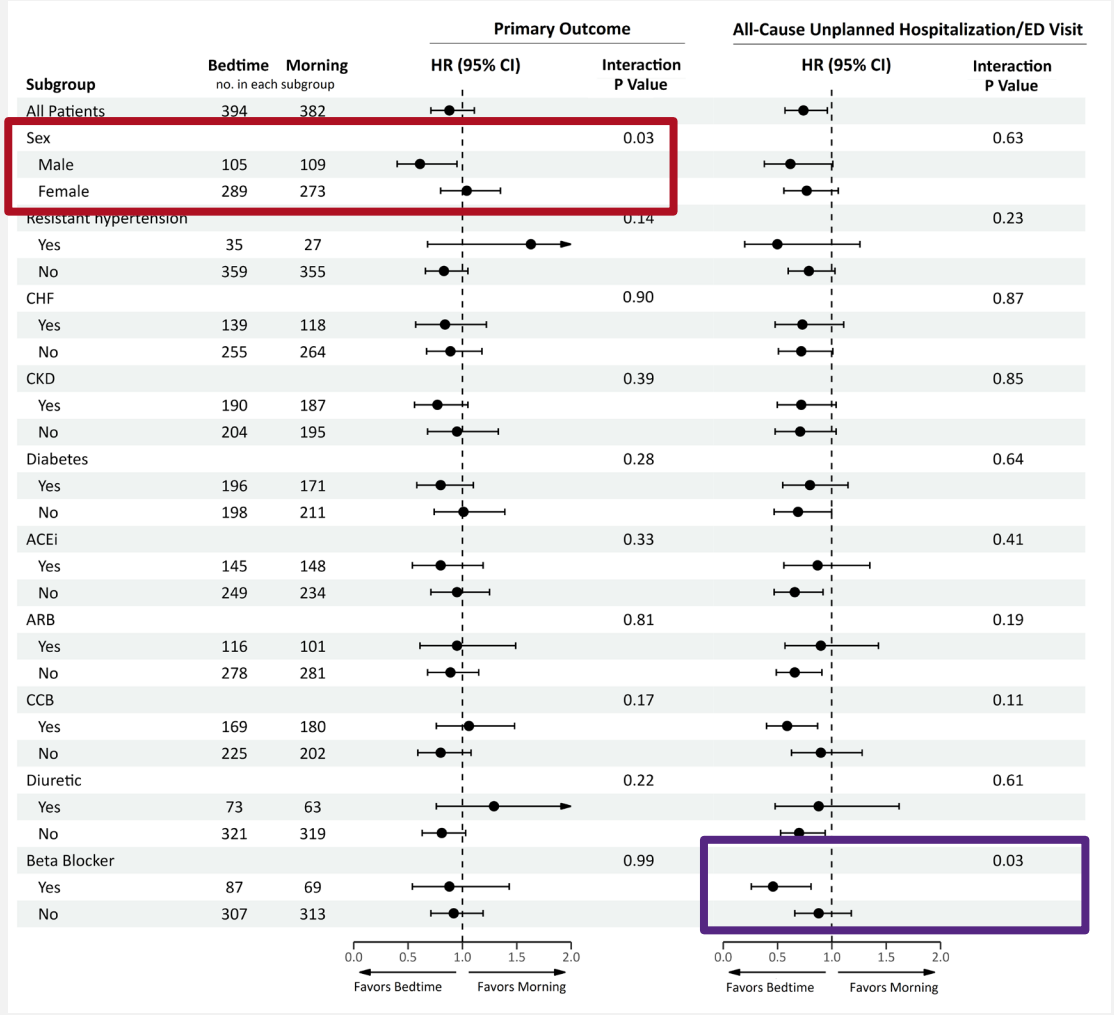
Secondary Outcomes

- **No difference in any outcome** other than first occurrence of all-cause unplanned hospitalization/ED visits. Post hoc, treating hospitalization/ED visits as a continuous outcome and analyzing **ALL** hospitalization/ED visits via Poisson regression, the RR is not significant – i.e. (**ARR, 0.87; 95% CI, 0.71-1.07; p = 0.20**)

Outcome	Bedtime N = 394		Morning N = 382		HR/RR (95% CI)	P Value
	n (%)	Rate/100 patient-yr	n (%)	Rate/100 patient-yr		
Secondary – Efficacy						
Primary Outcome Components						
All-cause mortality	157 (39.8)	28.7	157 (41.1)	30.7	0.89 (0.71 - 1.11)	0.29
Hosp/ED for stroke	3 (0.8)	0.5	7 (1.8)	1.4	0.40 (0.10 - 1.57)	0.19
Hosp/ED for ACS	2 (0.5)	0.4	2 (0.5)	0.4	0.93 (0.13 - 6.51)	0.94
Hosp/ED for CHF	8 (2.0)	1.5	6 (1.6)	1.2	1.26 (0.44 - 3.63)	0.67
All-cause unplanned hospitalization/ED visits	**107 (27.2)**	**22.6**	**128 (33.5)**	**30.0**	**0.74 (0.57 - 0.96)**	**0.02**
Secondary – Safety						
Falls/Fractures						
Non-vertebral fracture	9 (2.3)	1.7	10 (2.6)	2.0	0.84 (0.34 - 2.07)	0.71
Fall in the past 30 days	53 (15.4)	-	54 (15.9)	-	0.97 (0.67 - 1.42)	0.89
Cognitive/Behavioural						
Deteriorated cognition	32 (9.3)	-	35 (10.3)	-	0.92 (0.57 - 1.48)	0.72
Problem behaviours	50 (14.5)	-	42 (12.4)	-	1.13 (0.75 - 1.71)	0.55
Use of antipsychotic Rx or physical restraints	64 (18.6)	-	84 (24.7)	-	0.74 (0.53 - 1.03)	0.07
Indicators of depression or anxiety almost daily	56 (16.2)	-	48 (14.1)	-	1.11 (0.75 - 1.64)	0.61
Use of anti-anxiety Rx	25 (7.2)	-	23 (6.8)	-	1.06 (0.60 - 1.87)	0.84
Use of bedtime sedative	30 (8.7)	-	27 (7.9)	-	1.11 (0.66 - 1.87)	0.69
Other						
Partial or Full thickness skin ulcers (stage 2-4)	31 (9.0)	-	37 (10.9)	-	0.83 (0.51 - 1.33)	0.44
Urinary incontinence	302 (87.5)	-	287 (84.4)	-	1.04 (0.88 - 1.22)	0.68

Subgroups

- **Bedtime administration favored in males for the primary outcome** (interaction p value 0.03) and **beta-blocker users for all-cause unplanned hospitalization/ED visit** (interaction p value 0.03). However, we had 20 subgroup analyses – two of these could easily have shown a statistically significant interaction by chance alone.



Conclusions

For hypertensive patients with no history of glaucoma:

1) Antihypertensive medications can be safely taken at bedtime
2) No additional cardiovascular benefit is conveyed from doing so

Blood pressure medication should be taken whenever you are least likely to forget it

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www.PragmaticTrials.ca

The Pragmatic Trials Collaborative

Measuring What Matters