THINGS I'D LIKE TO STOP DOING, BUT CAN'T

MEDS Conference, Jan. 27|2018

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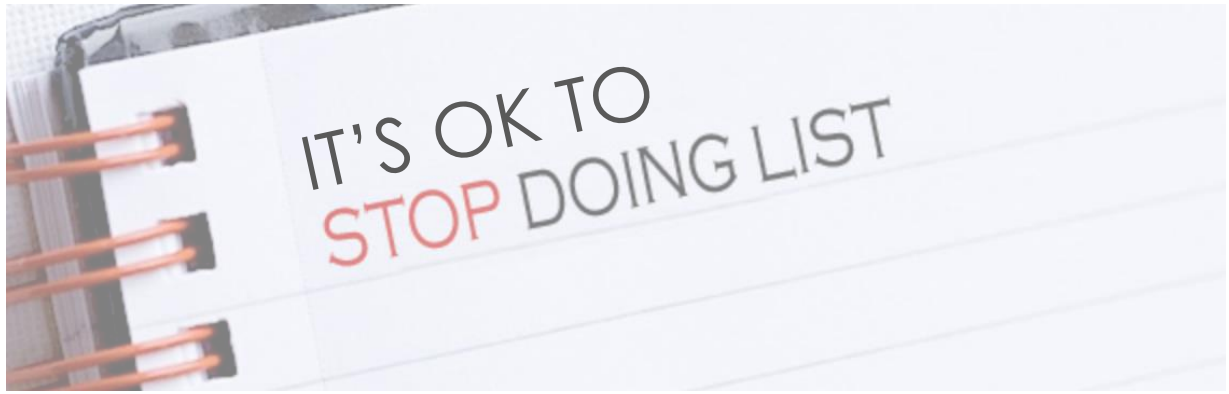
WE ARE ALL INDIVIDUALS

…and so are our patients

You don't need to follow me! You don't need to follow anybody!

https://www.youtube.com/watch?v=DHDnqQ_mCBA (James McCormack)

HERE'S WHAT'S TO COME…



1. Keeping beta-blockers on board post-MI
2. Using ICS in COPD
3. Aggressive target-shooting in DM2
4. Doing silly post-treatment initiation testing
5. An "automatic stop" laundry list

β-BLOCKERS POST-MI

Clinical Outcomes with β-Blockers for Myocardial Infarction: A Meta-analysis of Randomized Trials

Am J Med 2014;127:939-953

- ***The premise:*** many of the data to support use of BB post-MI predate reperfusion and contemporary medical therapy with statins and antiplatelet agents (esp. DAPT)
  - 66 RCTs → n = 102,003
    - **Reperfusion-era trials:** > 50% of patients received reperfusion either with thrombolytics or with revascularization or aspirin/statin

RESULTS IN A (COMPLICATED) NUTSHELL

Table 2 Landmark Analyses: β-Blockers vs Controls (From Fixed-effect Model)

	Death	CV Death	Sudden Death	MI	Angina	Stroke	Heart Failure	Cardiogenic Shock
Events at 30 days								
Pre-reperfusion	0.87 (0.79, 0.96)	0.86 (0.77, 0.96)	0.82 (0.59, 1.13)	0.81 (0.63,1.04)	0.89 (0.83, 0.95)	2.96 (0.47, 18.81)	1.06 (0.97, 1.16)	1.03 (0.87, 1.21)
Reperfusion era	0.98 (0.92, 1.05)	1.00 (0.91,1.10)	0.94 (0.86, 1.01)	0.72 (0.62, 0.84)	0.81 (0.66, 1.00)	1.09 (0.91, 1.30)	1.10 (1.05, 1.16)	1.29 (1.18, 1.41)
Events between 30 days and 1 year								
Pre-reperfusion	0.79 (0.71, 0.88)	0.84 (0.71, 1.00)	0.61 (0.49, 0.76)	0.77 (0.64, 0.91)	0.94 (0.75, 1.18)	1.54 (0.60, 3.95)	1.07 (0.91, 1.27)	1.88 (0.51, 6.96)
Reperfusion era	1.50 (0.53, 4.21)	1.50 (0.53, 4.21)	NA	0.71 (0.23, 2.25)	1.03 (0.72, 1.48)	4.00 (0.45, 35.79)	3.83 (1.56, 9.41)	NA

Am J Med 2014;127:939-953

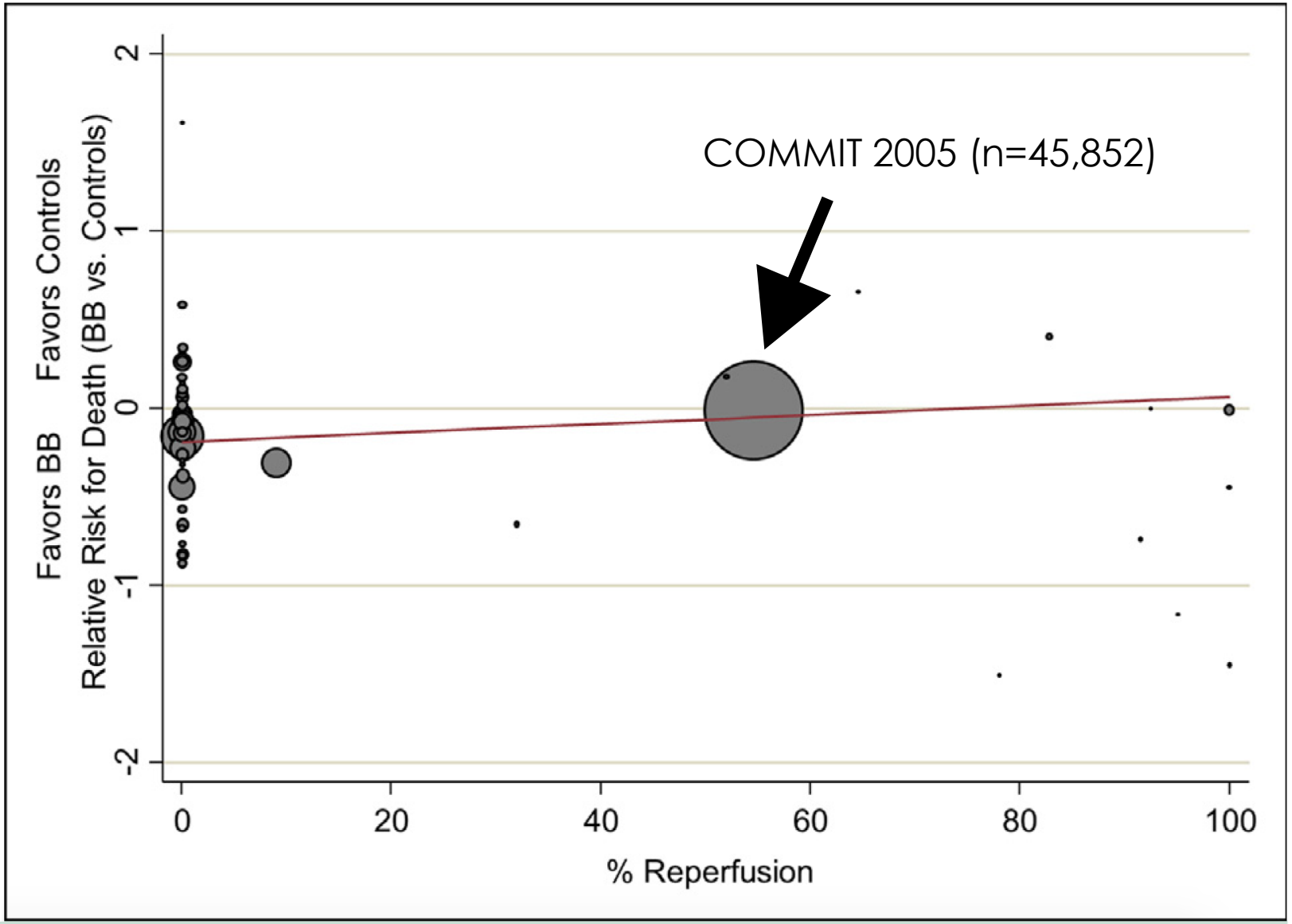


Figure 13 Meta-regression analysis of the relationship of percentage of patients with reperfusion therapy on the risk ratio of mortality with β-blockers.

Am J Med 2014;127:939-953

MORTALITY AS REPERFUSION INCREASES

(**note:** "reperfusion era" mostly driven by one study)

PARTING PERSPECTIVES

1. **Review: β-blockers do not reduce mortality in myocardial infarction in the reperfusion era**

ACP Journal Club

Ann Intern Med Mar 17, 2015

- *"The conclusions are solid and should influence future clinical guidelines that are the basis for quality-of-care indicators."*
- *"The findings of this meta-analysis should challenge the clinical guideline recommendation for routine administration of BB as mandatory STEMI treatment."*

2. **Author reply to Letter to the Editor** (*Am J Med 2014*)

- *"…for beta-blocker use in myocardial infarction, there is evidence of absence or absence of evidence, and neither is a good enough justification to continue current indiscriminate prescription patterns."*

LOOKING BACK IN TIME

Long-term β-blocker Therapy After Myocardial Infarction in the Contemporary Era: A Systematic Review

Jenny Hong[1], BSc(Pharm), ACPR and Arden R. Barry[2,3], BSc, BSc(Pharm), PharmD, ACPR

- **Inclusion criteria:**

1. RCTs or **observational cohort studies** with propensity scoring;

2. Investigated patients on BB therapy post-MI at discharge compared to patients not on BB and

3. Published ≤10 years

RESULTS (continued)

- 8 cohort studies of β-blocker versus no β-blocker therapy included[3-10]
- Median study population was 1838 and duration ranged from 1-5 yr
- All-cause mortality:
  - 2 smaller studies showed a significant reduction in all-cause

CONCLUSIONS

- The majority of contemporary studies identified did not demonstrate a reduction in death or MACE with long-term β-blocker therapy in patients post-MI without left ventricular dysfunction
- In the absence of a present-day RCT, this evidence imparts uncertainty regarding the current standard of care
- Therefore, it is not unreasonable to discontinue β-blockers after 1 year in post-MI patients with a preserved LVEF

STOPPING A β-BLOCKER POST-MI

- BB withdrawal syndrome
  - ~5% in the general population (e.g. HTN)
  - up to 50% in patients with angina

WHO?

(assuming no systolic CHF)

1) Bradycardia or hypotension & no angina
2) "Do I still need to be on all these meds" & no angina
3) >1 year post-MI & no angina → actively deprescribe?

Knowing that…

HOW?

- Gradually, if possible, over a few weeks to ⬇ risk of precipitating angina/MI
- No strict rules, but taper of ~10-14 days is reasonable to avoid symptoms of acute withdrawal
- My approach → cut dose in half q1-2w
  - e.g. metoprolol 50mg BID →
    25mg BID X 1-2 weeks →
    12.5mg BID X 1-2weeks → stop

UCH Clinical Pearls 2008
www.rxfiles.ca

ICS IN COPD:
MORE HARM THAN GOOD

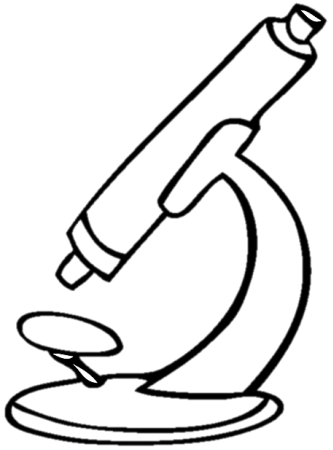


Table 2 Comparison between the NNT to prevent a COPD exacerbation and the NNT to induce pneumonia properly computed from the corresponding cumulative incidences (CIs) for recent trials of the fluticasone-salmeterol combination inhaler (ICS) versus a long-acting bronchodilator

			COPD exacerbation			Pneumonia		
			CI at end of study			CI at end of study		
	Study	Time span for NNT	ICS	No ICS	NNT	ICS	No ICS	NNT
n=7435	TORCH[1]	3 years	0.922*	0.945*	44	0.196	0.133	16
n=7435	INSPIRE[4]	2 years	0.578†	0.590†	83	0.094	0.049	22
n=2573	Kardos[3]	44 weeks	0.47	0.55	13	0.045	0.014	32
n=2573	Ferguson[5]	1 year	0.58	0.66	13	0.07	0.04	33
n=2573	Anzueto[6]	1 year	0.60	0.67	14	0.07	0.02	

Since then…

Suissa S. *Thorax* 2013;68:540–543.

ICS IN COPD:
MORE HARM THAN GOOD

FLAME study

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

N Engl J Med 2016;374:2222-34

- n=3362 (75% were GOLD stage D)
- **Results:**
  - **0.21** less exacerbations/pt/yr for LAMA+LABA
  - Pneumonia: **NNH = 63 for LABA+ICS**
- So, *vs.* LABA+ ICS, the LAMA+LABA combo is…
  - Modestly better (AECOPD) in the highest risk patients
  - Safer
  - Cheaper ($70-90 vs. $75-160)

WISDOM study

N Engl J Med 2014;371:1285-94

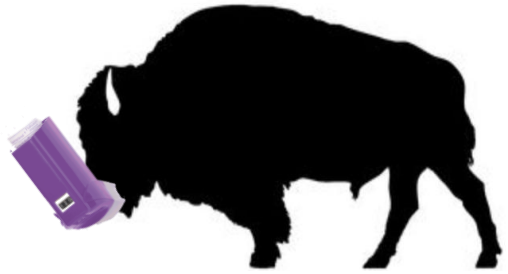
- n=2485 (baseline FEV1 = **34%**)
- Salmeterol + tiotropium + fluticasone X 6 weeks, then… **continue or stop fluticasone** X 12 months

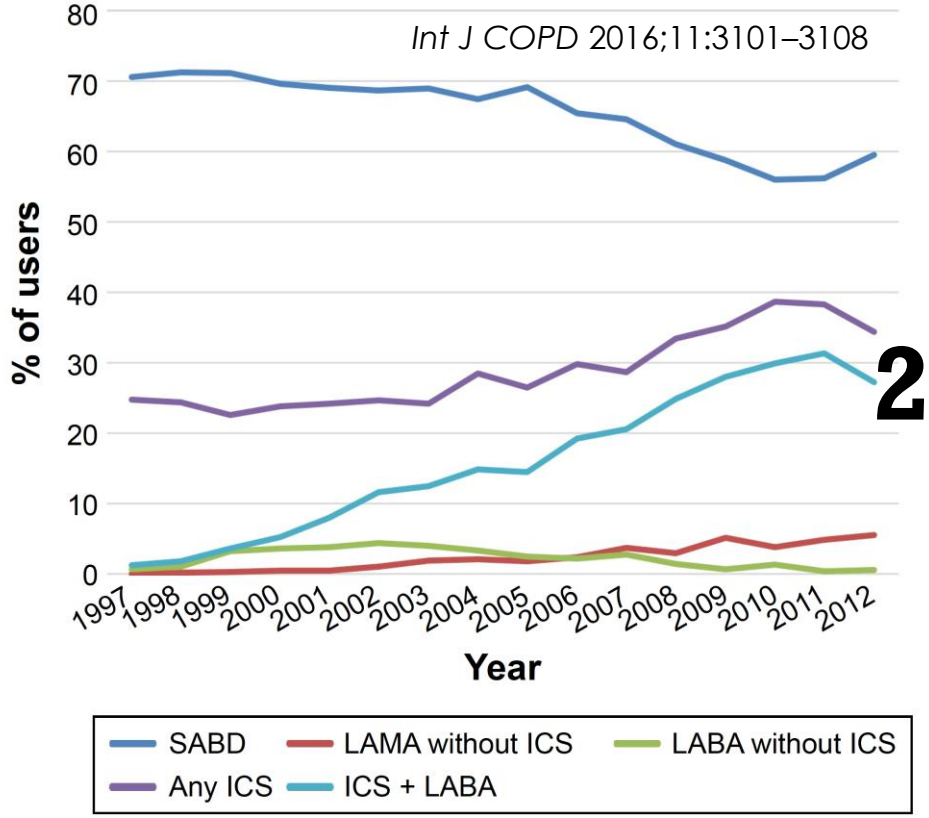
1+1+1 = 2

- **Results** (AECOPD, dyspnea, QoL):
  - Taking fluticasone away was **NO WORSE** than keeping it on board

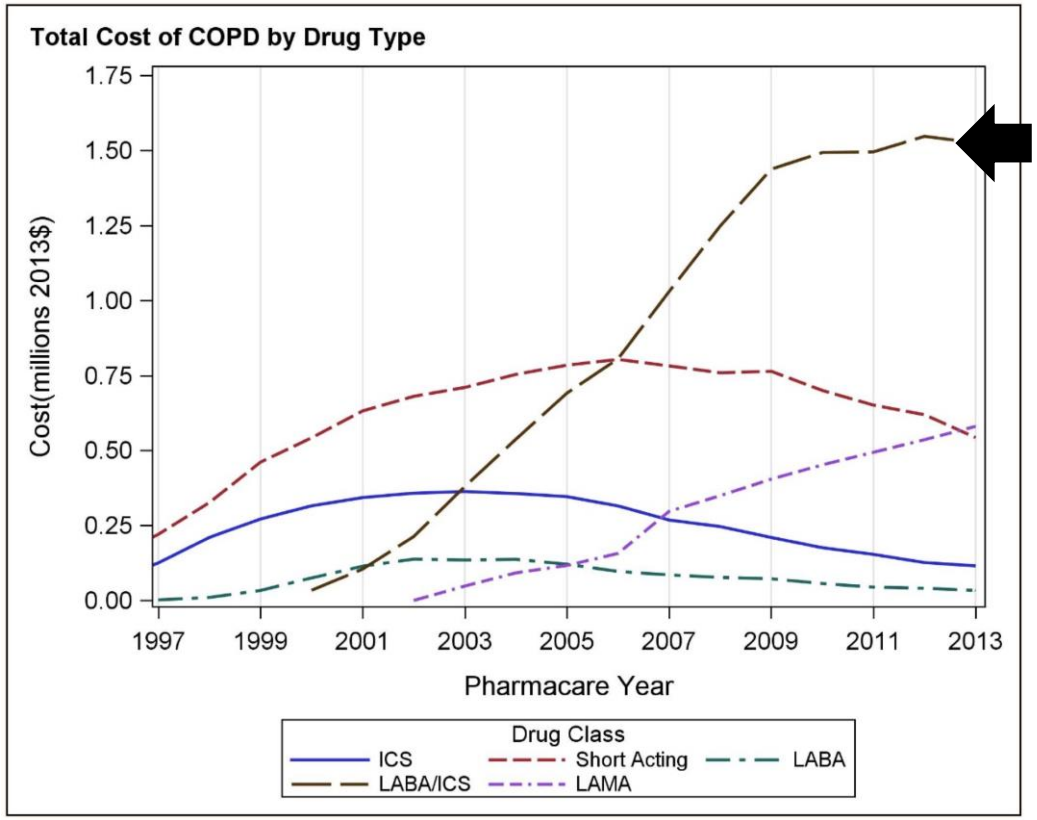
With the exception of those who also have documented asthma, it's difficult to justify the use of ICS for patients with COPD

ICS IN COPD:
HOW ARE WE DOING IN MB?





27%



ICS+LABA

54.4%

of COPD med costs

Figure 1 Classes of first medications after diagnosis by year.

*

++ money for nothing

ICS IN COPD:
IT WAS LIKE THAT WHEN I GOT HERE

- Don't be afraid to stop an ICS for COPD prescribed by a respirologist or added during admission

HOW?

- **WISDOM approach?**
  - e.g. fluticasone 1000mcg → 500mcg (6 wk) → 200mcg (6 wk) → stop (need for 2 separate inhalers… LABA and ICS)
  - "Smoothness" of taper dictated in part by the type of inhaler used
  - Is this really necessary knowing how modestly they perform**?**
- **Don't do it during an exacerbation**
- **Caution on coincidences**
- **Ask about dyspnea/rescue inhaler use**/exacerbations at visits over the next few months

TARGETS IN DM2:
DRIVING HARD TO THE HOOP

1. Aiming for an **A1c <7%** for anyone with DM2 >65 yrs of age
2. Aiming for a **BP <130/80** for anyone with DM2

TARGETS IN DM2:
RESULTS OF DRIVING HARD TO THE A1C HOOP

Glycemic Control for Patients
Our Evolving Faith i

René Rodríguez-Gutiérrez, MD,

This evidence reported no significa
transplantation/renal death, blindness, or neuropathy. In t
100%) and guidelines (95%) unequivocally endorsed bene
cardiovascular mortality, or stroke; however, there is a co
infarction.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)
	Assumed risk	Corresponding risk		
	Control	In-tensive glycaemic con-trol versus conventional glycaemic control		
All-cause mortality Follow-up: median 24 months	95 per 1000	95 per 1000 (87 to 103)	RR 1 (0.92 to 1.08) **no difference**	34325 (24)
Cardiovascular mortal-ity Follow-up: median 27 months	45 per 1000	48 per 1000 (42 to 55)	RR 1.06 (0.94 to 1.21) **no difference**	34177 (22)
Non-fatal myocardial in-farction Follow-up: median 60 months	48 per 1000	41 per 1000 (37 to 47) 7 per 1000	RR 0.87 (0.77 to 0.98)	30417 (14)
Non-fatal stroke Follow-up: median 54.6 months	29 per 1000	29 per 1000 (25 to 35)	RR 1 (0.84 to 1.19) **no difference**	30003 (13)
Amputation of lower ex-tremity Follow-up: median 65.1 months	13 per 1000	9 per 1000 (6 to 12) 4 per 1000	RR 0.65 (0.45 to 0.94)	11200 (11)
End-stage renal disease Follow-up: median 93.6 months	16 per 1000	14 per 1000 (11 to 17)	RR 0.87 (0.71 to 1.06) **no difference**	28145 (8)
Hypoglycaemia - Severe hypoglycaemia Follow-up: median 12 months	29 per 1000	64 per 1000 (45 to 91) 35 per 1000	RR 2.18 (1.53 to 3.11) **big difference**	28794 (17)

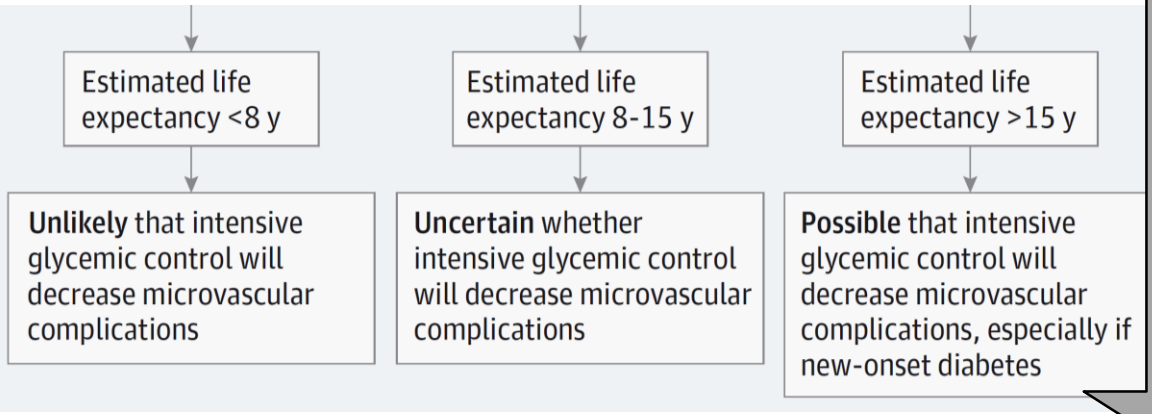
Circ Cardiovasc Qual Outcomes. Sept 2016;9
CDSR 2013, Issue 11. Art. No.: CD008143

TARGETS IN DM2:
RESULTS OF DRIVING HARD TO THE A1C HOOP

Care of the Aging Patient: From Evidence to Action

Polypharmacy in the Aging Patient
A Review of Glycemic Control in Older Adults With Type 2 Diabetes

JAMA 2016;315(10):1034-1045



Increased risk of severe hypoglycemia by **1.5-3X** appears immediately (not to mention ↑ meds, ↑ $, ↑ testing)

Type 2 Diabetes: What after Metformin, Dalhousie CPD Academic Detailing Service, March 2016
http://www.medicine.dal.ca/departments/core-units/cpd/programs/academic-detailing-service.html

Table 1: Lifetime Risk for Endstage Renal Disease in T2DM*[7]

A1C levels	Lifetime Risk for Endstage Renal Disease¥			
	Age of Onset			
	45yr	55yr	65yr	75yr
	%			
7	2.0	0.9	0.3	0.1
8	2.7	1.3	0.5	0.1
9	3.5	1.6	0.6	0.1
10	4.3	2.1	0.8	0.2
11	5.0	2.5	0.9	0.2

*For patients who develop end-stage renal disease, the average amount of time spent in this disease state was 5.2 years for those who were 45 years of age at diabetes onset, 4.6 years for those who were 55 years of age at onset, 4.0 years for those who were 65 years of age at onset, and 2.7 years for those who were 75 years of age at onset.
¥ Base-case results

Table 2: Lifetime risk of blindness due to diabetic retinopathy in T2DM*[7]

A1C levels	Lifetime Risk for Blindness¥			
	Age of Onset			
	45yr	55yr	65yr	75yr
	%			
7	0.3	0.1	<0.1	<0.1
8	1.1	0.5	0.2	<0.1
9	2.6	1.2	0.5	0.1
10	5.0	2.5	1.0	0.3
11	7.9	4.4	1.9	0.5

* For patients who become blind, the average amount of time spent blind was 11.0 years for those who were 45 years of age at diabetes onset, 8.3 years for those who were 55 years of age at onset, 5.2 years for those who were 65 years

"…for the majority of adults older than 65 years, the harms associated with an A1c target **lower than 7.5% or higher than 9%** are likely to outweigh the benefits"

TARGETS IN DM2:
DRIVING HARD TO THE BP HOOP

CPG	BP Target
CHEP 2016	**130/80**
CDA 2013	**130/80**
JNC-8 2014	140/90
ADA 2015	140/90
EUR 2013	140/85

<u>WHY are they aiming higher?</u>
Because no RCT has ever shown a target of 130/80 to reduce complications of DM2

www.hypertension.ca
JAMA. 2014;311(5):507-520
Journal of Hypertension 2013, 31:1925–1938
Can J Diabetes 2013;37:S31eS34
Diabetes Care 2014;37(Suppl 1):S14-80

TARGETS IN DM2:
RESULTS OF DRIVING HARD TO THE BP HOOP

the bmj | *BMJ* 2016;352:i717

Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses

- 49 trials, including 73,738 participants

CONCLUSIONS

Antihypertensive treatment reduces the risk of mortality and cardiovascular morbidity in people with diabetes mellitus and a systoli
than 140 mm Hg. If systolic bloo
140 mm Hg, however, further tr
with an increased risk of cardio
observed benefit.

Will this finally change future guidelines?

→ **CHEP 2017 doesn't seem bothered**

XII. Treatment of hypertension in association with diabetes mellitus

Background. There are no changes to these guidelines for 2017.

FROM THE MINISTRY OF SILLY TESTS…

- Surrogate marker testing after treatment initiation that has become standard of practice:

1. BMD post-bisphosphonate
2. Albumin/Creatinine ratio post-ACEI/ARB
3. LDL post-statin

A PROPENSITY FOR DENSITY
THE OSTEOPOROSIS CANADA APPROACH

Should I monitor therapy? If so, how often?

CMAJ 2010. DOI:10.1503/cmaj.100771

For patients who are undergoing treatment, repeat measurement of bone mineral density should initially be performed after one to three years; the testing interval can be increased once therapy is shown to be effective.

Grade of recommendation: **?**

NONE (not even a Grade D for "consensus")

WHAT DO WE KNOW?

Fracture Intervention Trial (FIT)

secondary analyses

Early detection of BMD loss not too important

Considerable variability in repeat testing

Most have a BMD gain in the end

- Chapurlat *et al.* (*Osteoporos Int* 2005)

  - Women with ↓ BMD (0 to -4%) after 1 year on alendronate had similar reductions in fracture risk after 3 years as those with ↑ BMD (0 to +4%) after 1 year

- Bell *et al.* (*BMJ* 2009) (*Can Fam Phys* 2010:56,1299)

  Alendronate increased BMD 0.013 g/cm^2 per year but individuals' readings varied by a similar amount (0.012 g/cm^2, standard deviation). Alendronate resulted in "sufficient" (≥0.019g/cm^2) increases in hip BMD for 97.5% of patients after 3 years.

Monitoring bone mineral density in postmenopausal women after starting a potent oral bisphosphonate is unnecessary and, because of the potential to mislead, is best avoided

WHEN ACEIs & ARBs ARE IN THEIR ELEMENT…

IF: → ACEI or ARB on board for HTN with ↑ ACR, and
→ BP is well-controlled

We already have them on the right drug **+** RCTs **did not** ↑ dose based on ACR **➡** Don't check ACR

?

- What would we do differently with an ACR?
  - Prognosis?
  - Cue for renal referral?

} OK, sure, but not frequently & **not to drive dose adjustments**

THE ARBITRARILY CHOSEN HOLY GRAIL

- RCTs DIDN'T target LDL, nor did they ↑/↓ meds to meet targets, nor did they compare one LDL target to another
  - e.g. primary prevention trial LDLs and CV events (www.rxfiles.ca), using ~10mg atorvastatin equivalent:

	CARDS	ASCOT	WOSCOPS	AFCAPS	MEGA
LDL reduction:	3.0→2.1	3.4→2.3	5→4.1	3.9→3	4.1→3.3
CV event RRR:	36%	37%	30%	38%	34%

BOTTOM LINE:

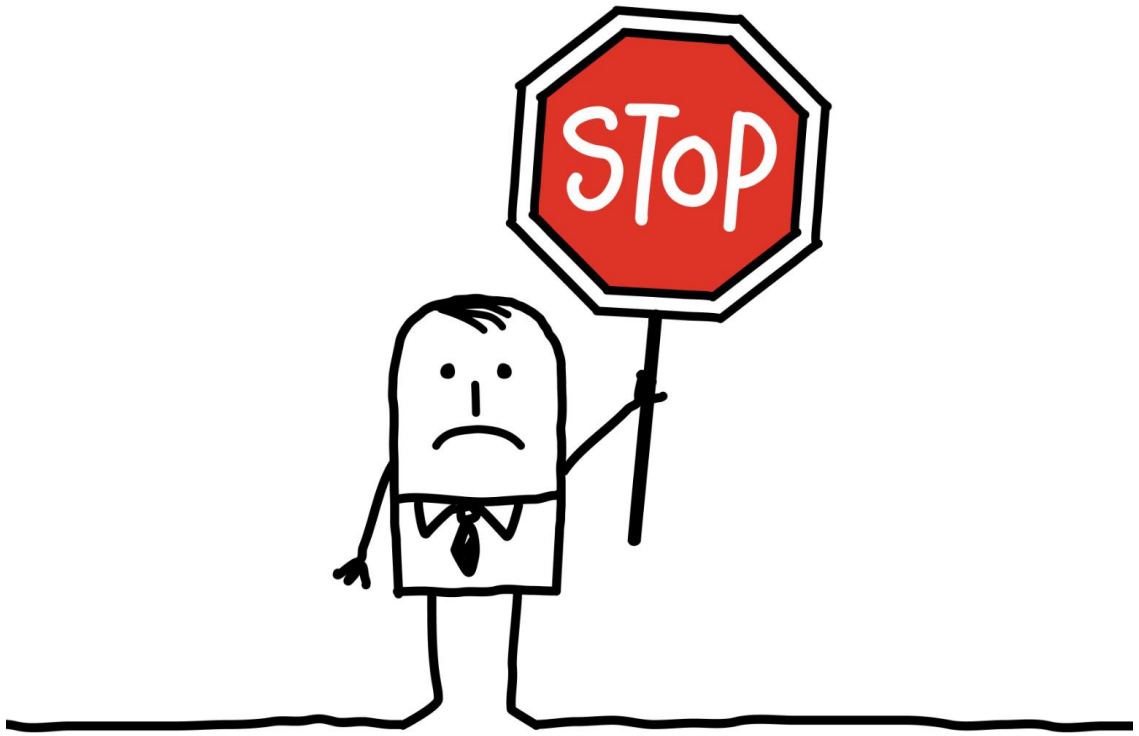
TOP 2015

X DO NOT target specific lipid levels

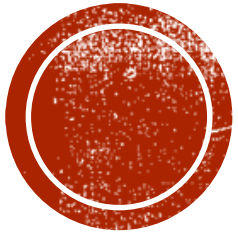
X DO NOT repeat lipid level testing for a patient on a statin

www.topalbertadoctors.org

A FEW EXTRA AUTOMATIC STOPS TO CONSIDER:



1. Recommending blanket vitamin D + calcium supplementation for all menopausal/post-menopausal women
2. Feeling compelled to use DAPT beyond 3 months in those with annoying bleeding issues
3. Asking for regular home BG testing in patients with diabetes not on insulin
4. Relentlessly trying to make resistant insomnia better with medication
5. Taking salt away from hypertensive patients
6. Pushing to maximum BB & ACEI doses in systolic HF for those with low-normal BP



QUESTIONS ?

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