Update in Outpatient Medicine November 9, 2019

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Disclosures

- Stock Holdings
  - Abbott Labs
  - Abbvie
  - Bristol Myers Squibb
  - Proctor and Gamble
  - Walgreens

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Topics

- Diabetes mellitus
  - Dose de-escalation
  - Guideline changes
  - New agents
  - Benefits beyond glycemic control
- Lipid lowering beyond statins in high risk patients
- Cost Effectiveness of Statins in Primary Prevention
- OTC Meds and DOACs
- Colorectal Cancer Screening in Younger patients and Surveillance in patients with low risk adenomas

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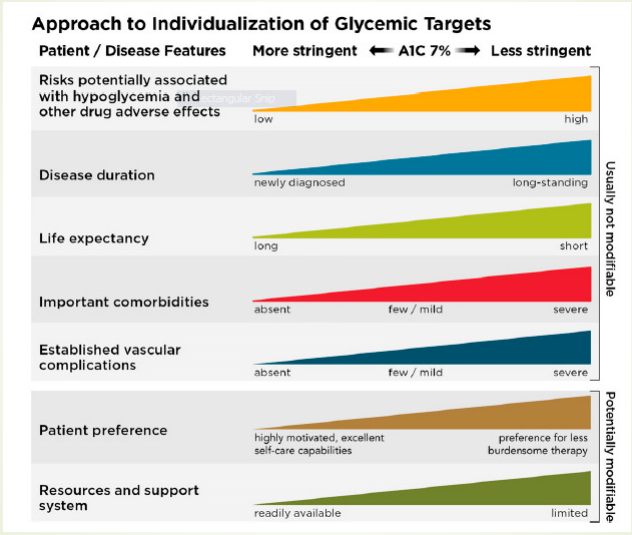

Less stringent controls (<8%) in some patients may be appropriate Grade B

Diabetes Care 2019;42(Suppl 1)S61-70

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Use and Discontinuation of Insulin Among Adults Aged 75-79 with Type 2 Diabetes

- Longitudinal cohort study of 21,531 patients with Type 2 DM from Kaiser Permanente Northern California aged 75 and followed for 4 years
- Assessed presence of co-morbidities and functional status
- Baseline insulin use 18.9%
  - Mean duration of insulin 7.9 years

JAMA Intern Med published online 9/23/2019

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Figure 2. Cohort Health Status Definition Compared With American Diabetes Association (ADA) Guideline Definition

Status	Cohort Health Status Definition	ADA Guideline Health Status Definition
Good Health 51.3% of cohort	0-1 Comorbidities 2 Comorbidities + any reported weekly exercise (comorbidities include CVD, stroke, retinopathy, CKD stage II-IV, COPD, and CHF)	0-2 Comorbidities with intact functional status (comorbidities include arthritis, cancer, CHF, depression, COPD, falls, HTN, urinary incontinence, CKD stage ≥3, MI, and stroke)
Intermediate Health 40.1% of cohort	2 Comorbidities + reported no weekly exercise >2 Comorbidities Use of a walker	≥2 IADL impairments >2 Comorbidities Mild to moderate cognitive impairment
Poor Health 8.6% of cohort	Any indicator of end-stage disease, including home oxygen use, metastatic cancer, and CKD stage V, including patients on hemodialysis Dementia	Any end-stage disease, including CHF stage III-IV, oxygen dependent, CKD with HD, and metastatic cancer Moderate to severe cognitive impairment or ≥2 ADL dependencies

Mortality rate in cohort during follow-up

7.4%

21.4%

52.4%

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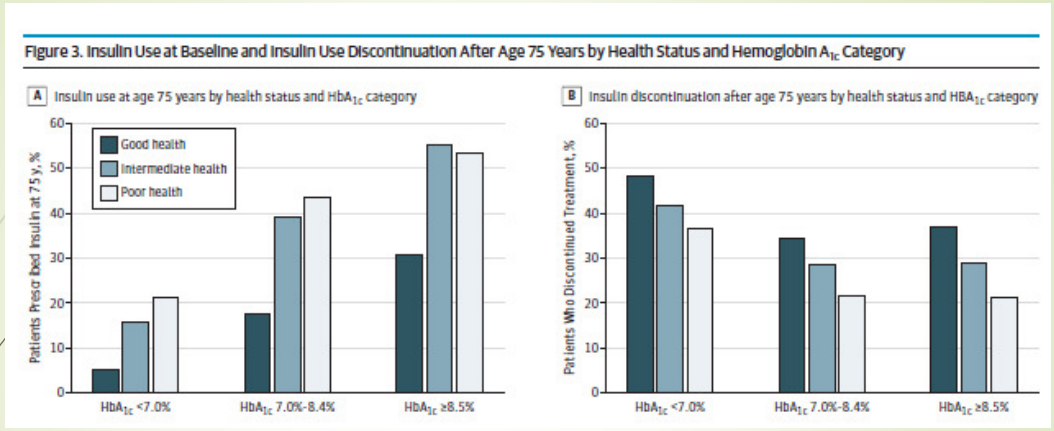

Insulin simplification 4.7% 7.8% 10.9%

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Insulin Use and Discontinuation in the Elderly

- Current guidelines recommend individualized glycemic targets based on health status
- This cohort study demonstrates greater use of insulin in patients with poor health status
- This cohort study demonstrates less discontinuation of insulin in those patients with tight control and poorer health status compared to those in good health
- Insulin is costly and carries the risk of hypoglycemia in the elderly
- There is an opportunity to consider appropriateness of current regimens, based on health status, in the elderly

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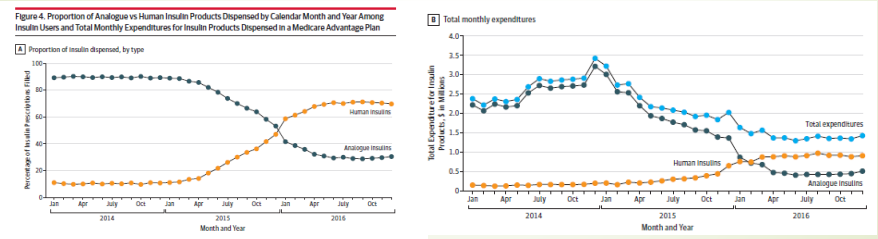
Implementation of Health Plan Switch From Insulin Analogs to Human Insulin

- 14,635 patients managed by CareMore changed insulin regimens
  - Ideal candidates were using 2 or more insulin injections/day, receiving basal and prandial injections, > 50 units/day, history of non-adherence and no recurrent hypoglycemia
  - Recommended initial dose of human insulin was 80% of prior total insulin dose of either 70/30 pre-mixed insulin or NPH
    - If using 70/30- 2/3 of daily dose before breakfast and 1/3 before dinner



JAMA 2019; 321(4):374-384

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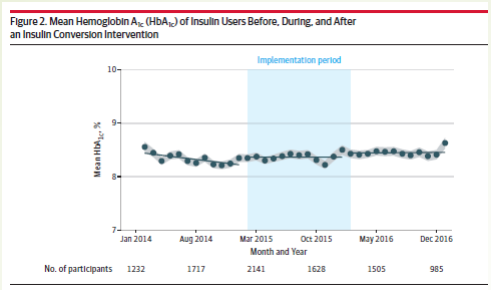

Increase HgBA1C of 0.14% likely not clinically significant in Medicare age patients

No increase in hypoglycemic or hyperglycemic events

NS increase in mortality in non-switch group (likely confounders)

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Lifestyle Modification and Long Term Clinical Outcomes with Diabetes

- Real world study of 19,293 patients care for in large Boston based academic health system
- Reviewed electronic health record documentation of diet, exercise or weight loss counseling using natural language processing
- Treatment assessment for 2 years after cohort entry
  - Mean follow up 5.4 years after the treatment assessment period
- Primary outcome-time to first CV event
- HgA1C decreased 1.8% in patients receiving at least monthly counseling vs. 0.7% in patients with less frequent counseling

Diabetes Care published online 8/1/19
https://doi.org/10.2337/dc19-0629

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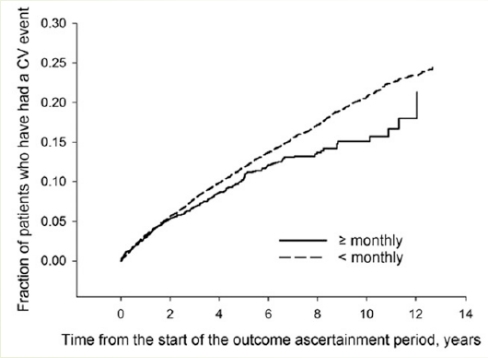

- Implementation is resource intensive
- Potential for group visits, telehealth

ARR at 10 years 5%
NNT 20

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Pharmacologic Approaches to Glycemic Treatment

- GLP-1 receptor agonists preferred over insulin for most type 2 diabetics (i.e. HbA1C < 11%)
  - **GRADE B recommendation**
- SGLT-2 inhibitors or GLP-1 receptor agonists recommended for type 2 diabetics with known CVD
  - **GRADE A recommendation**
- SGLT-2 inhibitors recommended for type 2 diabetics with CVD and high risk for CHF
  - **GRADE C recommendation**
- SGLT-2 inhibitors or GLP-1 receptor agonists recommended for type 2 diabetics with CKD

Diabetes Care 2019;42(Suppl 1)

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Association of Second-line Anti-diabetic Medications with CV Events in Type 2 DM

- Retrospective cohort study of 132,737 insured adults with Type 2 DM who started second line ADM therapy with a second line ADM with or without metformin.
  - Study conducted from April 2011-September 2015
  - 5.5% of patients had a history of CVD prior to starting second line ADM
- Primary outcome based on time to first cardiac event
  - Defined as hospitalization for CAD, CHF, CVA, PAD

doi:10.1001/jamanetworkopen.2018.6125

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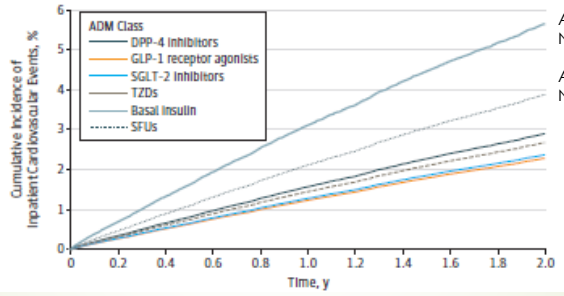
Figure. Adjusted Cumulative Incidence of First Cardiovascular Event After Starting the Second-line Antidiabetic Medication (ADM) Among Insured Adults With Type 2 Diabetes, by ADM Class



Adjusted HR basal insulin 2.03
NNH at 2 years 37

Adjusted HR Sulfonylurea 1.36
NNH at 2 years 103

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Oral Semaglutide vs. SQ Liraglutide and Placebo in Type 2 DM (PIONEER4)

- 711 patients randomized to oral semaglutide, SQ liraglutide or placebo
- HbA1c 7-9.5% on stable dose of metformin with or without and SGLT-2
- Exclusions: eGFR < 60 ml/min, proliferative retinopathy requiring treatment, pancreatitis, non-protocol DM/obesity meds
- Oral semaglutide 3 mg x 4 weeks, 7 mg x 4 weeks, then 14 mg
- Must be taken fasting with up to 4 ounces of water, no food or beverage for at least 30 minutes, as food impairs absorption of oral semaglutide
- Primary outcome: Change in HbA1c at 26 weeks
- Secondary outcomes: Change in bodyweight at 26 weeks, change ion HbA1c at 52 weeks, change is FBG 26-52 weeks, % reaching HbA1c of < 7%, weight loss of 5% or 10%

Lancet 2019;394:39-50

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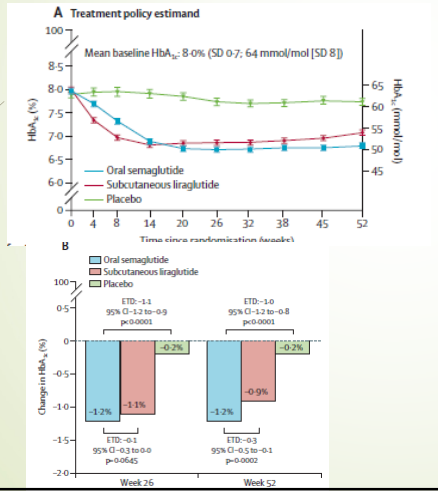
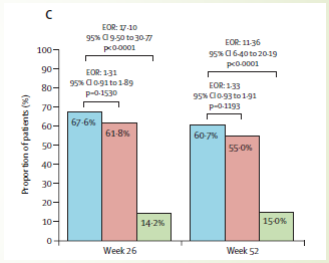
Glycemic control





Proportion of patients HbA1c < 7%

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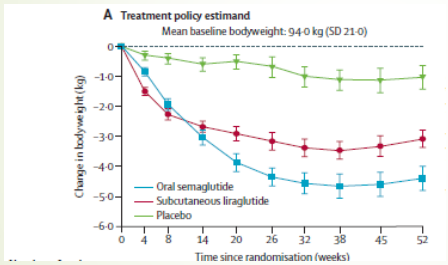
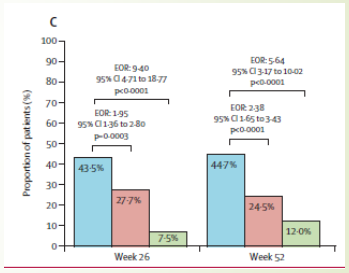
Weight Loss





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- Oral semaglutide more effective than SQ liraglutide in lowering HbA1c at 52 weeks
- Oral semaglutide more effective than SQ liraglutide at 26 and 52 weeks for weight loss
- Important to instruct patients on how to take medication correctly
- Rates of adverse events for oral semaglutide
  - Nausea 20%
  - Diarrhea 15%
  - Nasopharyngitis 14%
- Rates of discontinuation 11% oral semaglutide vs. 9% SQ liraglutide vs. 4% placebo

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Efficacy and safety of once weekly semaglutide vs. daily canagliflozin added to metformin SUSTAIN 8 Trial

- 788 patients aged 18 or older with type 2 DM and HbA1c 7-10.5% on at least 1500 mg metformin randomized to semaglutide 1 mg SQ once weekly vs. canagliflozin 300 once daily
- Primary endpoint was change in HbA1c at 52 weeks
- Secondary endpoint was change in bodyweight at 52 weeks

Lancet Diabetes Endocrinol published online 9/17/19

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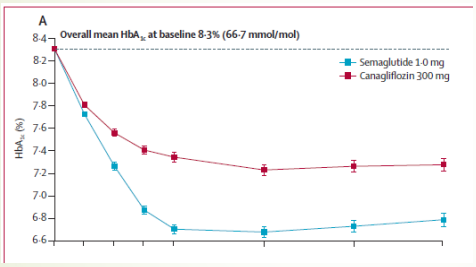

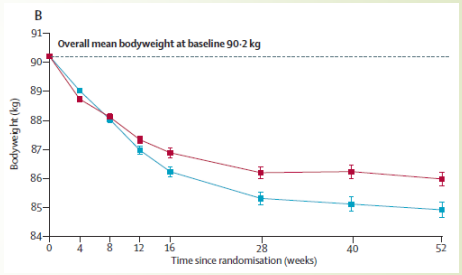

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	Semaglutide	Canagliflozin
HbA1c < 7%	66%	45%
HbA1c < 6.5%	53%	24%
Weight loss 10% of greater	22%	9%
Discontinuation of treatment	10%	5%

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Use of SGLT2 inhibitors and risk of major CV events and CHF: Scandinavian register based cohort study

- Cohort study from registry data from Denmark, Norway, and Sweden
- 25,988 eligible new users of SGLT2 Inhibitors and 94,411 new users of DPP4 inhibitors
- Median follow up 1.4 years
- Primary outcomes-major CV events (MI, CVA, CC death) CHF event (hospitalization or death
- Secondary outcome-all cause mortality and individual components of major CV events.

BMJ 2019;366:l4772

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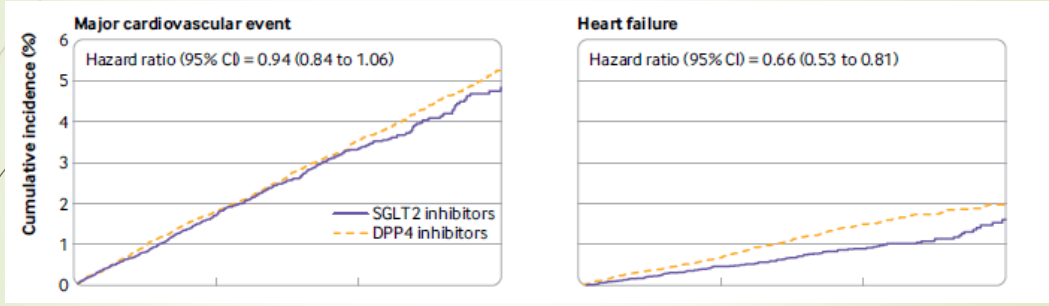

Meta-analysis demonstrated benefit (HR 0.86) in patients with established ASCVD
81% of cohort without ASCVD

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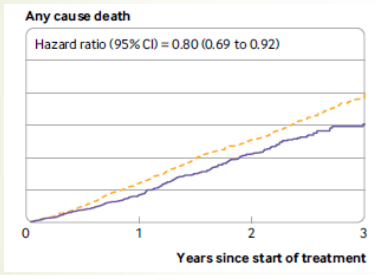

- Intention to treat an analysis demonstrated reduction in CHF and all cause mortality, but not major ASCVD event.
- As treated analysis demonstrated larger HF and mortality benefit and a reduction in major ASCVD event

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Summary- Diabetes Mellitus Update

- Oral semaglutide now approved by FDA and will be on the market soon
- Expensive, similar to injectable GLP-1 agonist
- GLP-1 agonist now recommended for most Type 2 diabetics before insulin
  - Expensive
  - Human insulin less expensive and for most Type 2 diabetics as effective without increased adverse events
- Patients taking SGLT-2 inhibitors have lower CHF risk
  - Less impact on glycemic control than GLP-1 agonists
- Sulfonylureas have cost benefits but some increased risk for CV events

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Effect of Simvastatin-Ezetimibe Compared with Simvastatin Monotherapy after ACS in Patients ≥ 75 Secondary Analysis IMPROVE-IT Trial

- 18,144 patients randomized within 10 days of ACS to simvastatin 40 mg monotherapy - vs. simvastatin 40 mg plus ezetimibe
  - LDL 50-125 mg/dL without history of lipid lowering or 50-100 mg/dL if on Rx
- Primary endpoint- CVD death or major adverse cardiac event defined as non-fatal MI, unstable angina leading to hospitalization, revascularization 30 days after index ACS, non-fatal CVA.

JAMA Cardiol 2019;4(9):846-854

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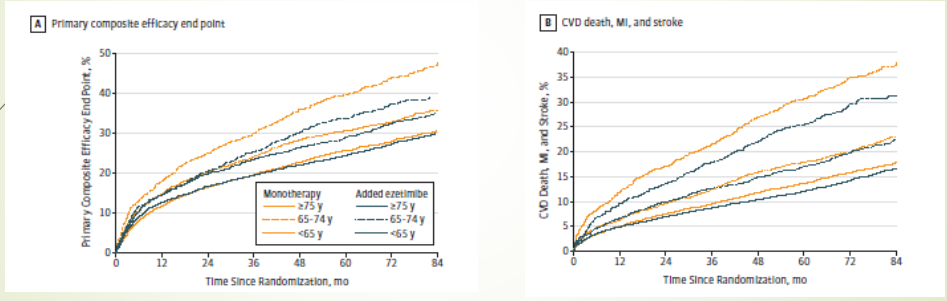

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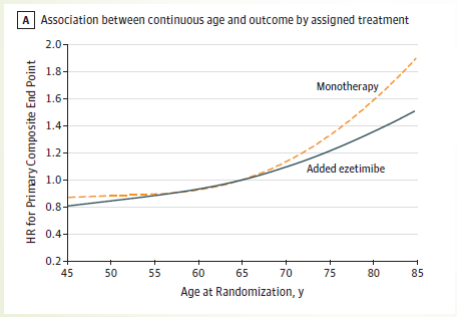

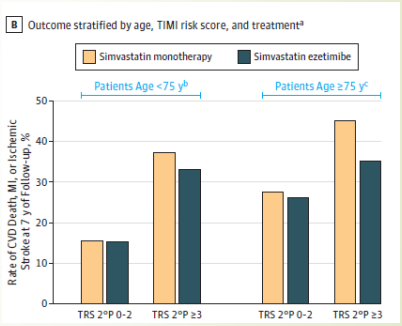

No difference in adverse events by age

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Effect of PCSK9 Inhibitor Evolocumab on Total CV Events in Patients with CVD A Prespecified Analysis from the FOURIER Trial

- 27,564 patients aged 40-85 with prior MI, CVA, or PAD
  - LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL while taking optimized statin therapy
- Randomized to SQ evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo
- Primary endpoint time to composite CV death, MI, CVA, hospitalization for unstable angina
  - Secondary endpoint- above minus unstable angina
- Median follow up 2.2 years

JAMA Cardiol. 2019;4(7):613-619

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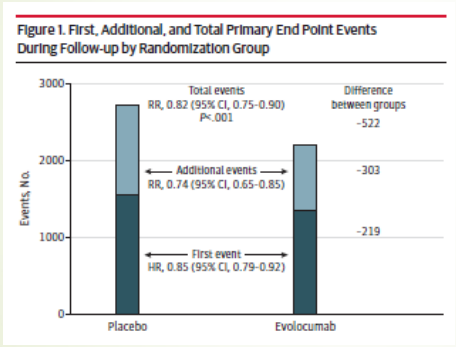

89.5% of trial patients had no events
5.7% had a single event
3.5% had two events
1.4% had 3 or more events

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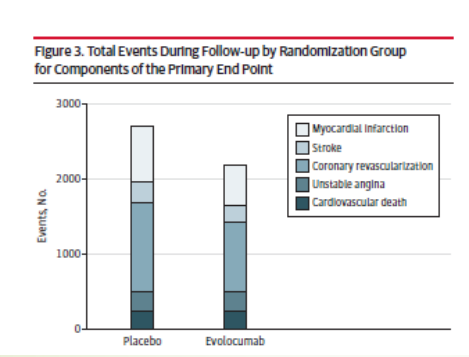

- For every 1000 patient treated for 3 years
  - 22 First events prevented
  - 52 Total events prevented

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Updated Cost-effectiveness Analysis of Evolocumab in Patients with Very High-risk ASCVD as defined by the 2018 ACC/AHA Guideline

- Updated cost-effectiveness analysis based on 60% price reduction in October 2018
- Patients had very high risk ASCVD with LDL ≥ 70 mg/dL despite maximally tolerated statin therapy
  - Only 5-6% patients received ezetimibe
- Modeled different scenarios considering baseline risk
  - 4.4 events per 100 patient years based on FOURIER clinical trial patients at VHR
  - 6.4 events per 100 patient years based on patients in usual clinical practice
  - 12.3 events per 100 patient years representing the usual clinical practice rate multiplies by the 2 fold risk since in VHR patients in the FOURIER Trial

JAMA Cardiol 2019;4(7):691-695

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ACC/AHA Guideline VHR Criteria

- History of multiple ASCVD events (recent ACS, History of MI or ischemic stroke, symptomatic PAD)
- 1 major ASCVD event and multiple high risk conditions
  - Age 65 or greater
  - Current smoking
  - Familial hypercholesterolemia
  - CHF
  - DM
  - HTN
  - CKD
  - Prior revascularization (CABG or stent)
  - LDL greater than 100 mg/dL despite maximal therapy

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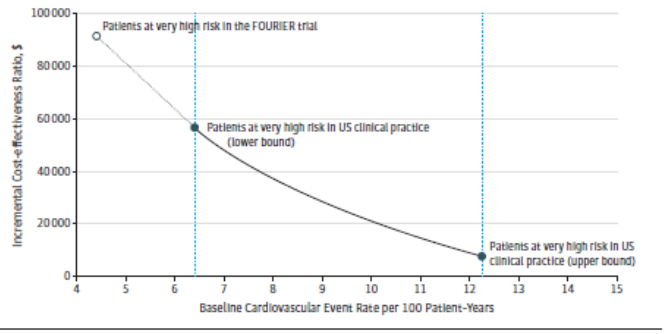
Figure. Incremental Cost-effectiveness Ratio as a Function of Baseline Cardiovascular Event Rate



Cardiovascular events include myocardial infarction, ischemic stroke, and cardiovascular death. An annual evolocumab list price of $5850 was used. FOURIER indicates the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk trial.

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- Ezetimibe is generic and inexpensive and should be used first in VHR patients with persistently elevated cholesterol
- FOURIER Trial enrolled few patients with ezetimibe added to a statin
- Patients with persistently elevated cholesterol and VHR probably benefit from adding a PCSK9 Inhibitor
- Cost effectiveness has significant variation based on risk estimates

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Cost Effectiveness of LDL Cholesterol Level Guided Statin Therapy in Patients with Borderline CV Risk

- Microsimulation model of 4 statin treatment strategies
  - Treat all patient with 10 year absolute risk ≥ 7.5%, diabetes, or LDL ≥ 190 mg/dL
  - Treat patients with 10 year absolute risk 5.0-7.4% and LDL 160-189 mg/dL
  - Treat patients with 10 year absolute risk 5.0-7.4% and LDL 130-159 mg/dL
  - Treat all patients with 10 year absolute risk ≥ 5.0%
- Modeled treatment with moderate intensity statin for borderline risk patients
- Modeled lifetime treatment in 100 simulated cohorts of 1 million patients aged 40 at baseline

JAMA Cardiol. 2019;4(10):969-977

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Figure 3. Cost-effectiveness of Moderate-Intensity Statin Therapy

ICER (Cost per QALY gained)	Assessment
≥$150 000 per QALY	Not cost-effective
$50 000-$150 000 per QALY	Intermediately cost-effective
$0-$50 000 per QALY	Highly cost-effective
Dominant	Cost saving

Men aged 40 y	Baseline 10-y Risk, %	Baseline LDL-C Level, mg/dL			
		<100	100-129	130-159	160-189
	<1.0	Dominated	151 325	51 759	29 677
	1.0-2.4	Dominated	60 493	17 471	Cost saving
	2.5-4.9	Dominated	44 715	8219	Cost saving
	5.0-7.4	71 038	6410	Cost saving	Cost saving
	≥7.5			Cost saving	Cost saving

Women aged 40 y	Baseline 10-y Risk, %	Baseline LDL-C Level, mg/dL			
		<100	100-129	130-159	160-189
	<1.0	Dominated	7 885 907	103 222	45 493
	1.0-2.4	Dominated	381 475	85 107	16 989
	2.5-4.9	7 667 685	138 336	28 087	Cost saving
	5.0-7.4				
	≥7.5				

Men aged 50 y	Baseline 10-y Risk, %	Baseline LDL-C Level, mg/dL			
		<100	100-129	130-159	160-189
	<1.0				
	1.0-2.4	Dominated	156 204	43 592	
	2.5-4.9	Dominated	33 230	7039	Cost saving
	5.0-7.4	157 413	14 408	3727	Cost saving
	≥7.5	122 524	6437	Cost saving	Cost saving

Women aged 50 y	Baseline 10-y Risk, %	Baseline LDL-C Level, mg/dL			
		<100	100-129	130-159	160-189
	<1.0	Dominated	Dominated	214 360	61 287
	1.0-2.4	Dominated	140 001	51 773	17 147
	2.5-4.9	Dominated	123 694	29 306	7840
	5.0-7.4		29 364	2185	Cost saving
	≥7.5				

Men aged 60 y	Baseline 10-y Risk, %	Baseline LDL-C Level, mg/dL			
		<100	100-129	130-159	160-189
	<1.0				
	1.0-2.4				
	2.5-4.9	Dominated	146 320		
	5.0-7.4	Dominated	22 629	Cost saving	Cost saving
	≥7.5	42 223	Cost saving	Cost saving	Cost saving

Women aged 60 y	Baseline 10-y Risk, %	Baseline LDL-C Level, mg/dL			
		<100	100-129	130-159	160-189
	<1.0				
	1.0-2.4	Dominated	Dominated	142 111	40 226
	2.5-4.9	Dominated	124 853	29 804	6029
	5.0-7.4	Dominated	69 893	466	Cost saving
	≥7.5	188 836	20 576	Cost saving	Cost saving

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- Treating patients with borderline risk and LDL ≥ 160 is likely cost saving
- Treating patients with borderline risk and LDL 130-159 may be cost saving in men and likely cost effective in women
- Assumes 50% adherence and 0.5%/year development of diabetes
- Long time horizon for cost savings to develop
- Unclear if CAC scoring would increase efficiency
- Need patient centered approach

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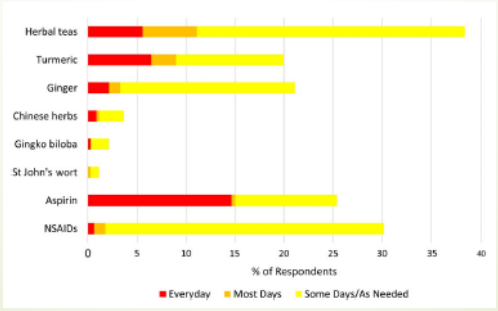
Prevalence and Knowledge of Potential Interactions Between OTC Products and Apixaban

- Surveyed patients treated at UCLA and UCSF who were taking apixaban
- 34% of patients reported daily or almost daily use of at least one OTC product with potential interaction with a DOAC
  - 27.2% additional patients reported some use of OTC meds with potential risk



J AM Geriatr Soc 00:1-8,2019

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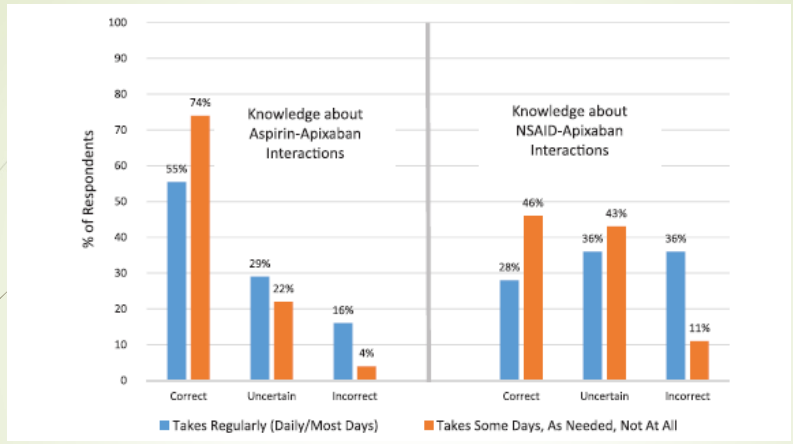

Increasing use of DOACs
Emphasizes the need to question about use of OTC meds

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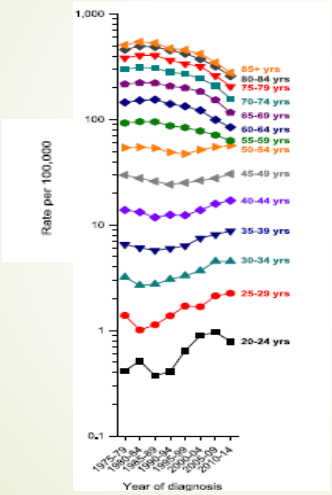
Colorectal Cancer Screening for Average Risk Patients-2018 Update from the ACS



- Qualified recommendation to start screening at age 45
- Stool based test or structural exam
- Incidence 45-49 31.4/100,000
- Incidence in 50-54 58.4/100,000

Doi:10.3322/caac.21457 Available online at cacancerjournal.com

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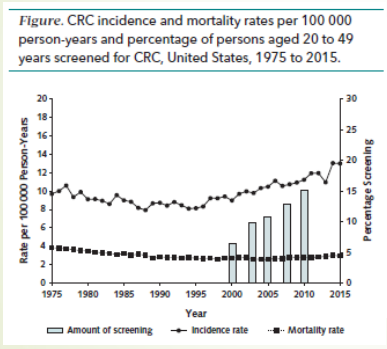

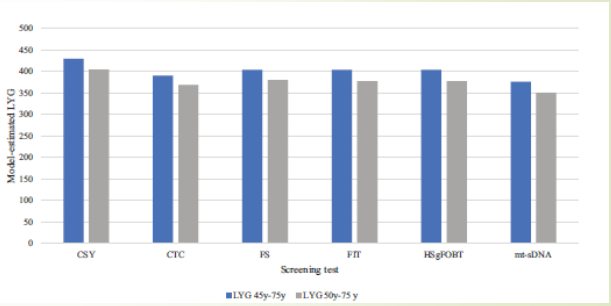

Estimated 16 additional life years per 1000 patients screened for colonoscopy vs. FIT

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Colorectal Cancer Screening- ACS Guideline

- Colon cancer rates increasing in younger patients, but still much less common than patients > 50
- Significant decrease in CRC rates in older patients likely related to screening
- ACA mandate to fully cover cost of CRC screening is based on USPTF (age ≥ 50)
- Colonoscopy first strategy in younger patients costly to patients
- Models show similar impact in mortality reduction for colonoscopy first vs. FIT
- FIT first offers less opportunity to reduce CRC incidence
- Cost of universal screening with a mix of colonoscopy and FIT at an estimated cost $250 per screen- estimated $5.5 billion or $6.1 million per death averted

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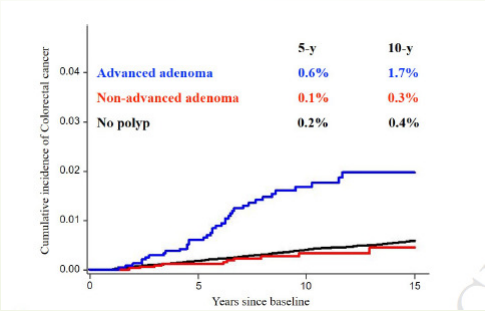
Long Term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps

- Follow up of 3 large cohort studies including 122,899 who underwent removal of conventional adenomas
- Median follow-up 10 years



https://doi.org/10.1053/j.gsdtro.2019.06.039

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Questions?

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