Research Viva

Contents

Research methodology – key concepts....3
Evidence based medicine....3
Study designs....3
Clinical trial phase....3
Sampling methods....3
Statistics basics....3
Bias....3
Meta analysis principles....4
Critical appraisal of a paper....4
Search engines....4
Audit cycle....4
Current EBM on key topics....5
IHD and stroke....5
Cardiovascular medication....6
STEMI....7
NSTE ACS....8
Stable CAD....10
1ry prevention of IHD....10
Atrial fibrillation....11
Diabetes....13
Prevention....13
Targets....13
Treatment....14
CVDr....16
Renal....17
Hypertension....17
Targets....17
Treatment....18
Heart failure....19
HFrEF....19
HFpEF....20

Devices....21
Dyslipidemia....21
Stroke....26
Nutrition....30
COPD....31
Bronchiectasis....32
IPF / ILD....32
SLE....32
NAFLD....33
IBD....33
Sepsis....33
Critical care....35
PCKD....35
Migraine....35
Toxicology....36
NEJM....37
LANCET....40
JAMA....42
BMJ....46
Sri lankan trials....47
Toxicology....48
Organophosphate....48
methHb....48
PCM....48
snake bite....48
Digitalis....49
Paraquat....49
Infections....49
DM, HTN, ASCVD....50

Research methodology – key concepts

Evidence based medicine

Study designs

Observational
Interventional

Real world data
Meta analysis, meta regression
Network meta analysis

Clinical trial phase

Pre clinical – animal
Clinical
I
II
III
IV

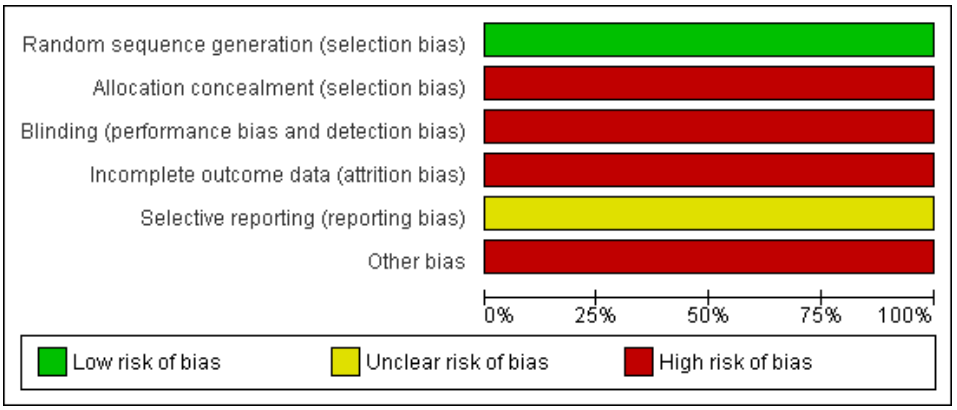
Sampling methods

Statistics basics

Bias

Selection – allocation concealment, random sequence generation
Performance – blinding of patients and personnel
Detection – blinding of assessor
Attrition – incomplete outcome data

Meta analysis principles



Critical appraisal of a paper

Search engines

Pubmed

Embase – need subscription

Cochrane library

- Reviews
- Trials
- Clincal answers

Audit cycle



Current EBM on key topics

IHD and stroke

	STEMI	NSTE ACS	Stable angina	Stroke
O2	AVOID, DETO2X			SOS
Aspirin	ISIS-2	**RISC, VASC**	**SAPAT** **PHS**	IST, CAST, WASID
Clopid	CLARITY-TIMI, COMMIT	CURE, CREDO	CAPRIE	CAPRIE, PRoFESS
Ticargrelor	PLATO	PLATO		-
Prasugrel	TRITON TIMI 38	TRITON TIMI 38		-
Asp + dipyr	-	-		ESPS-1, ESPS-2, ESPRIT, PRoFESS
Enoxaparin	ATOLL, ASSENT-3 Avoid fonda in PCI : OASIS-6	Fonda better :**OASIS-5**		-
Definitive	**PPCI**: PRAGUE, DANAMI, FASP, STAT, GUSTO-1b DES: EXAMINATION, COMFORTABLE AMI **TNK > rtPA**: ASSENT-2 **rtPA > SK** : GUSTO **SK > placebo**: ISIS-2 **BB**: METOCARD CNIC, EARLY BAMI / COMMIT	TIMACS for PCI timing TACTICS, VERDICT	**COURAGE** : PCI = OMT for mortality but gives better angina control	**rtPA**: NINDS-rtPA, ATLANTIS, ECASS-3 ENCHANTED, WAKE-UP **TNK**: EXTEND IA TNK **Thrombectomy:** MR CLEAN, ESCAPE, SWIFT PRIME, THRACE, EXTEND IA, REVASCAT DEFUSE-3, DAWN
DAPT	CLARITY TIMI, COMMIT, TRITON TIMI 38, PLATO, DAPT, PEGASUS TIMI 54, SMART DATE	CURE, CREDO, COMMIT		CHANCE POINT
Warfarin	-			AF: EAFT, ACTIVE-W
Apixaban	-			ARISTOTLE, AVERROES
Dabigatran	-			RE-LY
Rivaroxaban	ATLAS ACS TIMI 51			ROCKET-AF
Sx	-			**CEA**: NASCET, ECST

				PFO: CLOSE, REDUCE **LAAO**: PROTECT AF
BB	CAPRICON			
ACEi	SAVE, AIRE, VALIANT,			
MRA	EPHESUS, ALBATROSS, REMINDER			
Statin	MIRACL PROVE IT TIMI 22			SPARCL
Lipid	IMPROVE IT, FOURIER, ODYSSEY-LONG TERM			

Intra coronary alteplase during PCI does not reduce post procedure microvascular occlusion
UGIB rsik : clopid < ticar < prasu

Sleeping < 6h/day increase subclinical atherosclerosis

Cardiovascular medication

	IHD	HFrEF	HFpEF	HTN	DM neph	
Enalapril		CONSENSUS, SOLVD	-		DETAIL	
Captopril	VALIANT	SAVE			CSG	
Ramipril	AIRE				IDNT, IRMA	
Lisinopril						
Losartan						
Telmisartan						
Irbesartan						
Candesartan						
Valsartan	VALIANT					
Sacubitril valsartan						
Metoprolol						
Carvedilol						
Bisoprolol						
Nebivolol						
Atenolol						
Amlodipine						
Nifedipine						
Thiazide						
Spriono-lactone				PATHWAY-2 for resistant HTN		

STEMI

Fibrinolytics

SK – GISSI was the first trial to show efficacy of SK

ISIS-2

SK Vs aspirin Vs SK+aspirin Vs standard
28d mortality reduction 22% 24% 42% over control arm

GUSTO

SK Vs rtPA Vs SK+rtPA in addition to UFH and aspirin
rtPA offered mortality benefit at 30d over other groups
rtPA was first tried in GISSI-2 and TIMI-1. But failed due to too slow rtPA infusion

ASSENT-2

TNK Vs rtPA
Equal 30d mortality
Less non cereral bleeds and need for BT with TNK
1y FU – equality maintained

TNK : genetically modified version of rtPA. slower plasma clearance, better fibrin specificity, and high resistance to plasminogen-activator inhibitor-1

PCI

GUSTO-IIb

rtPA Vs angioplasty
superior in reducing composite of CV death, nonfatal reMI and non fatal stroke at 30d

PRAGUE-2 (SK Vs 90min)/ **DANAMI-2** (rtPA Vs 120 min)
Transfer for PCI within 90-120 min Vs on site SK/rtPA
SK/rtPA group also received rescue PCI

Antiplatelets

Aspirin

ISIS-2

P2y12i

CLARITY TIMI 28

Clopid addition to aspirin
Reduce 30d mortality without increased bleeding

TRITON TIMI 38

- PCI treated STEMI / NSTEMI
- Prasugrel Vs clopid as the 2nd antiplt for 12m
- Prasugrel increased bleeding. Equal mortality. Less composite 3 point MACE
- Avoid in past stroke / TIA, age > 75y, weight < 60y

PLATO

- Ticargrelor Vs clopidogrel in ACS for 12m
- Superior 3 point MACE and all-cause mortality
- No increase in bleeding : reversible ADP R inhibition, faster onset and offset of action, more potent antiplt efficacy
- More SOB and bradycardia – resemblance to adenosine

DAPT duration

PEGASUS TIMI 54

Asp + ticagrelor for 36m Vs 12m post PCI (DES)
Lesser CV events greater major bleeding

DAPT

asp + clopid/prasugrel for 30m Vs 12m post PCI (DES)
Less stent thrombosis but modest increase in bleeding
Increased bleeding was related to cancer and all cause mortality

SMART DATE

Asp + clopd for 6m Vs 12m or more post PCI (DES)
No difference in composite, increase in MI
Limitations – wide inferiority margin, most used clopid, adherence to protocol drugs low in 6m arm, open label

Anticoagulants

OASIS-6

Fonda > UFH after TNK. but increase thrombosis with PCI

ASSENT-3

Enox > UFH after TNK for STEMI

ATLAS ACS-2 TIMI-51

Riva+DAPT for ACS
Decrease CVE bu increase bleeding

APPRAISE-2

Apixaban + DAPT increases major bleeding, trial discontinued

COMPASS
Low dose riva + aspirin Vs either alone
Less CVE more bleeding

NSTE ACS

PCI timing
TIMACS
Early (<24h) Vs delayed PCI (> 36h)
Beneficial sp when GRACE > 140

TACTICS-TIMI 18
PCI in 4-48h Vs conservative (PCI if indicated or Ex ECG based)
High use of tirofiban
TIMI > 2 benefited CVE reduction

VERDICT
NSTE ACS
PCI < 12h Vs 48-72h
Equal outcome
Better outcome in the subgroup GRACE > 140

Antiplatelets
CURE
Clopid + asp Vs aspirin (as monoRx)
Superior in NSTEMI

COMMIT
STEMI (90%) and NSTEMI Non PCI Rx pts
Clopid added to aspirin
DAPT improved mortality
IV metoprolol mod to high dose – no difference in death / arrest. Increased cardiogenic shock.
Targeted HR 50 SBP 90. Did not exclude SBP 90

Anticoagulants
OASIS-5
Fondaparinux Vs enoxaparin
Non inferior efficacy, less bleeding
Increased stent thrombosis but easily overcome by the UFH bolus

ESSENSE
Enox > UFH
2 weeks
UA/NSTEMI

ACEI/ARB

SAVE	captopril	
VALIANT	valsartan = captopril	no benefit in combination
EPHESUS	epleronone	

.

.

LUNAR
Ritux no benefit in renal response

RITUXILUP

Stable CAD

Aspirin
SAPAT – superior for MI prevention
Aspirin trialist collaboration meta analysis

Physician health study – I, SCAD cohort – 87% reduction in ACS

Clopidogrel
CAPRIE
Clopd 75mg vs aspirin 325 mg/d
Clopid superior efficacy and safety in improving composite – CV death, stroke, MI

Statins
4S
Simvas reduce mortality in stable CAD (angina / past MI)

PCI Vs medical therapy
COURAGE – stable CAD optimal medical Rx Vs PCI + OMT
PCI – less angina high QoL. No difference in mortality at 3y

CABG Vs PCI
BEST – multivessel CAD.
PCI – increase non fatal MI and need for revascularization. But 40% wer DM+

1ry prevention of IHD

Aspirin
Physician health study-I **NEJM** 1989

- Male physcians
- Aspirin 325mg EOD
- Primary prevention of CVD – non significant CV death reduction, significant MI reduction (44%), no effect on stroke, non significant ICH increase
- 87% CAD reduction in those with stable angina
- Beta carotene arm --??

PHS-II : vit C and E do not prevent CVD, cancer or eye disease

Aspirin100mg od Vs placebo for 1ry Px of CVD

	ASCEND	**ARRIVE**	**ASPREE**
Study people	DM	> 55y mod CVDr	>70y healthy
1ry end point	Composite fo CV death, MI, stroke, TIA..	Composite ..	All cause mortality
Outcome	Benefit NNT 110 Increased bleeding – NNH 91 (mostly GI)	No benefit Major bleeding equal but Increased GI bleeding	Increase all cause mortality, mostly due to cancer related deaths
Limitations	Low PPI use	Low CV event rate	Need long term

DAPT for 1ry prevention

CHARISMA – in stable CAD people DAPT Vs asp – greater bleeding, no CAD reduction, small reduction in strokes

Statins for primary prevention

WOSCOPS – high lipids
JUPITER – high hsCRP
CARDS – T2DM

Atrial fibrillation

Rate Cx = rhythm control

AFFIRM trial (2002)

- High stroke risk non valvular AF in older adults. N 4000, FU 3.5 y
- BB / CCB / digoxin Vs anti arrhythmic by physician (drugs, RFA, MACE, pacing)
- Target HR 80 at rest and 110 at exercise
- Same stroke rates
- Non significant decrease in mortality with rate control, sp in > 65y, non HF pt groups
- Successfully cardioverted pts had the choice of discontinuing warfarin after 4 weeks of being in SR

RACE-II (2010)

- Permanent AF
- 600 pts
- Resting HR < 80 = < 110
- No difference in composite of (CV death, stroke, major bleeding, arrhythmic events, CHF.
- **Among secondary outcomes, strokes were lower with lenient strategy**

Stroke prevention

SPAF

Non valvular AF
Selection bias – warfarin CIn group allocated to aspirin arm. So less sicker people received warfarin

SPAF-1 W Vs P A Vs P
W – NNT 20
A – NNT 37
Limitation – low event rate, inflated RRR. Excluded > 75y people

SPAF-2 W > A

SPAF 3 fixed low dose W + A < W (2-3)
Similar major bleeds

ACTIVE-W

Non valvular AF
Asp + clopid Vs W
Equal beelding, better stroke reduction
DAPT was inferior in stroke reduction

ACTIVE A

Asp clopid Vs asp
Asp less bleeding
Asp clopid less strokes

NOAC trials for AF

- Double blind RCTs (RE-LY was open label)
- N 15000 – 20 000
- FU – 2y (2.8 in ENGAGE AF TIMI 48, 3.5y in ROCKET AF)
- Age – 70y, Men 60%, CKD III ~ 20%. Excluded CKD IV/V
- With increased risk of stroke. Baseline CHA2DS2VASc ~ 2 (~3 in ROCKET AF and ENGAGE AF TIMI 48)
- TTR in warfarin arm ~ 65%. Lower in ROCKET-AF (55%)

	RE-LY		**ROCKET-AF**	**ARISTOTLE**	**ENGAGE AF TIMI 48**	
	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
	150mg bd	110 mg bd	20mg od	5mg bd	60mg od	30mg od
Embolism	Less	Same	Same	**Less**	Same ?less	Same
Isch stroke	Less	Same	Same	Same	Same ?less	**More**
Hmrg stroke	Less	Less	Less	Less	Less	Less
ICH	Less	Less	Less	Less	Less	Less
GI bleeding	**More**	Same	**More**	Same	**More**	Less
Mjr bleeding	Same	Less	Same	**Less**	Less	Less
All cause mort	Same	Same	Same	**Less**	Same	Less

* all are in comparison with warfarin

* edoxaban 60mg is approved for stroke prevention, but not 30mg (less stroke reduction than warfarin)
Meta analysis of all trials, Compared with warfarin, NAOCs cause

1. Less embolism/stroke composite (by 19%) (mainly by reducing hemorrhagic stroke)
2. Less ICH
3. More GI bleeding
4. Less overall mortality (by 10%)

Stroke reduction
Superior Dabi 150 bd, apix, edox 60 od

Mjr bleeding
Superior dabi 110 bd, apix, edox

Rocket AF – same bleeding and stroke

LAAO – PROTECT-AF, PREVAIL : comparable to warfarin. Do if cannot anticoagulate.

Diabetes

Prevention

Pre DM □ DM

1. LSM – 53% reduction : DPP
2. Metformin – 31% reduction : DPP
   No benefit in > 60y
   Equal benefit to LSM in PHx GDM women (50%)
   Better benefit than LSM in BMI > 35
3. Lorcaserin – 19% reduction : CAMELLIA-TIMI 61

DPP – NEJM 2002
LSM (diet and 150 min exercise a week to achieve 7% LoW) Vs metformin 850 mg bd Vs placebo
For preDM (IFG, IGT), FU ~ 3y
LSM Vs metformin Vs conventional (standard advice)
Metformin reduced weight – might have mediated the benefit
LSM objective assessment difficult

CAMELLIA-TIMI 61 – lancet 2018
Lorcaserin 10mg bd Vs placebo, N = 12000
Age > 40y, BMI > 27, DM +/-
Reduce new DM by 19% in preDM and 23% in non DM
Reduced A1c by 0.33% in DM

Finnish Diabetes Prevention Study 2001
LSM Vs pt advice
IGT pts
58% reduction in new DM

Only finnish people

Targets

Study (N, yr, FU)	Pt Fx (age, DM, A1c, BMI)	Intensive Vs standard	Outcome	Comments
DCCT, 1500, 1993, 7	< 40y, new T1DM. w/o HTN	7.2, 9.1	Micro **70**% reduc	Young people, so macro were rare
EDIC, 1400, 2005, 11y	DCCT participants	~ 8.2% in both cohorts	Macro 42% reduc (57% for severe CVE)	
UKPDS-33, 3900, 1998, 10y (glib, glipi, metf, Insulin)	53, new, 7.1, 27.5	7, 7.9	Micro **25**% reduc Mostly retinopathy	BP arms ateno = capto 144 > 154 for micro, macro, death
ADVANCE, 11 000, 2008, 5 (gliclazide 30-120)	66, 8, 7.5, 28	6.5, 7.3	Death, macro – no diff. Micro 10% reduc, sp nephron	Small A1c difference Rosi only 17% BP arms (peri-inda) 136 > 142 for micro, macro, death
VADT, 700, 2008, 5.6	62, 12, 9.4, 32	6.9, 8.4	Death, macro, micro – no diff	Small N, high drop out
ACCORD, 10 000, 2009, 3.5	62, 10, 8.3, 32	6.5, 7.5	Death, macro – increased Micro not assessed	High rosi (91% Vs 57%) & low ACEi in intensive arm. More wt gain in intensive arm BP : 119 V 133. No benefit except transient stroke reduc. More AKI. Underpowered, advanced disease. LIPID- adding fenofibrate – no mortality reduction

Treatment

	Metformin	SU	AGI	Pioz	DPP4i	SGLT2i	GLP1RA
Hypo	No	Yes	No	No	No	No	No
Weight	Loss	Gain	Neutral	Gain	Neutral	Loss	Loss
MACE safety	Presumed	?	ACE	PROACTIVE	CARMELINA TECOS, EXAMINE, SAVOR-TIMI	EMPA REG CANVAS DECLARE	LEADER SUSTAIN-6 HARMONY ELIXA EXCSEL
CV event reduction (stat sig for superiority)	Presumed	?	No	PROACTIVE	None	EMPA REG CANVAS DECLARE	LEADER SUSTAIN-6 HARMONY

CV death reduction						EMPA REG	LEADER
HF	Neutral Avoid if decomp	High risk	Neutral	Moderate risk Pio - PROACTIVE Rosi – RECORD – increase HF	Inc HF hosp in SAVOR TIMI, EXAMINE	EMPAREG CANVAS Reduce hosp by 35%-33%	Neutral
CKD	Avoid < 30 1g if 30-45	More hypo	Neutral	Neutral	Reduce albuminuria. Low dose except lina	Not In if < 45 Retard : EMPAREG, CANVAS-R, CREDENCE DAPA-CKD	Retard LEADER, SUSTAIN-6 Exenatide: not if < 30
SE	GI		GI	Fluid retention, Oporosis		Amputation Genital infections KA	GI

DECLARE TIMI 58

17 000

FU – phone

MACE safety (CV death, MI, stroke), dual efficacy for CVD HF MACE

Tested for 2ry and 1ry prevention

Weight loss, HbA1c 0.2%? reduced SBP

MACE safe, but no reduction (superior design), reduced HHF. No reduction in CV death / MI / stroke / mortality. Reduces CVD/HHF composite in both 1ry and 2ry Px strategy

CVD benefit out of proportion to moderate HbA1c reduction

No rise in amputation, Founier

Rise in AKI and genital infection, DKA, major hypo, bladder cancer

	EMPA REG OUTCOME	**CANVAS**	**DECLARE TIMI 58**
Drug	Empagliflozin 10mg, 25 mg	Canagliflozin	Dapagliflozin
Year of pub	2015	2017	2018
N	7000	4000	17000
Population, % with ASCVD	A1c 7-10 (8.5) ~ 100%	A1c 7-10.5 60%	A1c 7-10.5 40%
FU			4.2y
1ry outcome	3 pt MACE	3 pt MACE	3 pt MACE
A1c reduction	0.24 – 0.36	0.58	0.42
BP reduction	4/2	3.9/1.4	2.7/0.7
Weight reduction	2	1.6	1.8 kg
MACE	Superior, NNT 62 (no dif in subgroups age < 65y and A1c > 8.5%)	Superior	Non inferior
HF hosp	Superior, NNT 71	Superior	Superior. Same in both 1ry and 2ry ASCVD Px groups
CV mortality	Superior, NNT 45	No difference	No difference

Renal	Decrease CKD progression	Decrease albuminuria and CKD progression	Decrease CKD progression
SE	High genital infections, AKI	Toe amputiations Genital infections	DKA (80% were on insulin) Genital infecitons
limitations	Benefits were seen only when the 2 arms (10mg and 25mg) were pooled and compared against placebo. Benefits not seen in subgrps age < 65y and A1c > 8.5%	Low ESKD event rate Low CKD prevalence in study group	

CV benefit in all these trials were seen as early as within 3 weeks!

Canagliflozin decrease BMD but doesn't increase # risk

Sotagliflozin for T1DM

When added to insulin improves glycemic control, but increases DKA

LEADER

Liraglutide
T2DM A1c > 7%, ASCVD+ or high risk
Reduce 3 point MACE reduce CV mortality and CKD progression
Limitations

- HbA1c reduced by --- but not below 7%
- Control arm – high SU use

AWARD-7

Dulaglutide Vs insulin glargine in T2DM
Dula retards CKD progression and proteinuria

UKPDS – 34 1998 Lancet

Metformin effects – beneficial on CVD and mortality
1700 new T2DM FU 10y
MF Vs other (LSM Vs other OHGs)

CVDr

DiRECT - Intensive LSM (low calorie diet and exercise) induces remission of T2 diabetes in obese people
Intervention - withdrawal of antidiabetes and antihypertensive drugs, total diet replacement (825–853 kcal per day formula diet for 12–20 weeks), stepped food reintroduction (2–8 weeks), and then structured support for weight-loss maintenance.
Follow up – benefit sustained to 2y

	No alb □ MIA	MIA □ ESKD / worsening proteinuria
T1DM	-	**Captopril** Vs placebo (Collaborative Study Group) **Enalapril = telmisartan** (DETAIL)
T2DM	**Perindopril**-indapamide (ADVANCE} **Trandolapril** Vs verapamil (BENEDICT) **Olmesartan** (ROADMAP) (all 3 were on HTN pts. No benefit in normotensives)	**Irbesartan** Vs amlodipine (IDNT), vs placebo (IRMA-2) **Losartan** Vs placebo/standard antiHTN (RENAAL)

Renal

Hypertension

Targets

SPRINT

- 9361, < 120 Vs 135-139, Anti HTN at treating physicians discretion
- > 50y, SBP > 130, high CVDr (clinical or subclinical ASCVD, Framingham > 15%, GFR 20-60)
- **Excluded DM and stroke** (ACCORD and SPS3-BP had already shown that in DM and stroke pts, intensive BP reduction was of no benefit)
- Also excluded GFR < 20, P'uria > 1g/d, GN, PCKD, EF < 35%
- FU : prematurely stopped at **3y** due to superior efficacy of intervention
- Population **~ 68y, fram ~ 20% achieved 121 vs 136**
- Primary outcome: **composite of ACS, stroke, HF, CV death -** less in intensive (NNT = 63)
- individual HF, CV death, all cause death reduced
- more AKI and hyperK and hypotension, cognitive decline in elderly
- **Limitations**
  1. DM, stroke excluded
  2. No Asians
  3. Premature discontinuation exaggerates treatment effects
  4. Automated BP meters reads BP 5-10 mmHg less than real
  5. Effect on cognition not assessed, too short
  6. Low proportion were on ASA and statin (~ 50%)
  7. Open label
  8. Polypharmacy. Individual drug effects not considered
  9. Premature discontinuation

SPRINT MIND – Follow up from SPRINT

Intensive BP control reduced MCI but not dementia

ACCORD BP
T2DM, high ASCVD
Intensive Vs standard
No advantage

What is the target BP for CKD pts?
140/80 ESC 2018.
Because ADVANCE BP showed it is better than > 140 SBP in DM-CKD
SPRINT showed lowering BP to 120 increases AKI and reduces GFR, also shown in ACCORD-BP
However, AHA recommends 130/80

Treatment

Diet

DASH trial 1997
Control Vs fruit and veg rich Vs fruit and veg rich and low salt low fat
BP control 3^{rd} > 2^{nd} > 1^{st} grou[s
Benefit within 2 weeks
Lasts for 6 weeks
Long term outcome not assessed
Best BP control in < 160/90 group

TONE 1998
1000
Low salt and weight loss improves BP control

ACEI and other drugs in comparison
LIFE 2002
Losartan Vs atenolol
For same BP reduction, losartan reduced mortality!

VALUE 2004
Valsartan inferior to amlodipine in BP control
No mortality difference

ALLHAT	ACCOMPLISH
2002	2008
Chlorthalidone, amlodipine, lisinopril Equal BP control and CVD reduction C – better SBP control, less HF, less stroke Doxazocin ithdrawn due to high mortalit	Benazepril + HCT Vs benazepril + amlodipine BH < BA Limitation – H inferior to C in efficacy

Thiazide like chlorthalidone, indapamide. Proven benefit for CVD benefit
Thiazide type HCT, chlorothiazide

Heart failure

HFrEF

1986	V-HeFT	ISDN+hydralazine reduce systolic HF. No mortality benefit. Trend+
1987	**CONSENSUS**	enalapril added to digoxin and diuretics in NYHA IV CCF
1991	V-HeFT-2	ISDN+Hydral Vs enalapril enalapril superior
1991	**SOLVD**	enalapril reduced mortality and HF hospitalization in NYHA II-IV EF < 35%
1992	**SAVE**	captopril reduces mortality by 19% in post MI **asymptomatic HF (EF < 40%)**
1994	**GISSI-3**	lisinopril reduces mortality in post MI with NL LVEF. Later meta-analysis – offset by hypotension and renal injury. Benefit in aSTEMI, Killip II/III, HR > 100
2000	HOPE	ramipril prevents HF in at risk (normal EF at present)
2001	ValHeFT	valsartan in NYA II-IV reduce symptoms and mortality. But no benefit in adding to ACEi
2003	VALIANT	valsartan = captopril. Post MI HF. No benefit in combining
2003	CHARM-preserved	candersartan in HFpEF. Reduces hospitalizations no mortality benefit
	CHARM-added	ACEi + candersartan is beneficial over ACEI alone
	CHARM- alternative	candersartan can replace ACEI
	ELITE-2	losartan = captopril
	HEAAL	losartan high dose (150mg od) Vs low dose (50mg od). Mild increase in mortality + hosp benefit and mild increase in hyperK, hypotension
2008	ON TARGET	telmisartan + Ramipril Vs telmi Vs rami. Combo no benefit. Tel = rami
2014	PARADIGM-HF	sacubitril + Valsartan Vs enalapril. Reduces CV mortality HF hospitalization and All-cause mortality. CV mortality reduction (?ARR) ~ 10% : like what enalapril achieved in CONSENSUS Used oa lower than normal enalapril dose

NYHA I included
Suspected increase in neprilysin by increasing beta amyloids
Post hoc analysis – sacu-val improves glycemic control – may be by increasing GLP-1

Sacubitril inhibits breakdown of BNP, bradykinin, adrenomedullin by neprilysin
Need for 36h interval after ACEi
Alone use increased HTN by potentiation on angiotensin

2018	PIONEER HF	sacu-val for acute HF after stabilization – greater reduction in NT pro BNP decline. Reduce rehospitalization but no effect on mortality
1999	CIBIS-II	bisoprolol Vs placebo NYHA III-IV. 34% mortality reduction
1999	MERIT HF	metoprolol succinate NYHA II-IV. 35% mortality reduction
2002	COPERNICUS	carvedilol NYHA III-IV EF < 25%. Mortality benefit
2003	COMET	carvedilol > metoprolol tartrate. NYHA III-IV. Lower metoprolol dose.
2004	SENIORS	nebivolol improves mortality. > 70y NYHA?
2008	BEAUTIFUL	ivabradine reduces mortality in NYHA EF < 40% only in the subgroup with **HR >** **70** and EF < 40% Sub group follow up – HF hosp reduced
2010	SHIFT	EF < 35%. Reduces admission and HF deaths, sp if HR is high Pt on BB with HR > 70. BB underused (below target dose). Same benefit would have been achieved by increasing BB dose

RALES 1999
Spiro
30% all cause mortiality reduciotn
Before BB use

EPHESUS-HF 2003
epleronone
post aMI HF, used BB
mortality benefit +

EMPHASIS (2011)
Chornic HF NYHA II-IV
Mortality reduction

HFpEF

CHARM preserved – reduce hospitalization. No mortality benefit
I preserved – irbesartan. No benefit
TOPCAT – spiro reduce hospitalization. No mortality reduction

Devices

COAPT - Mitraclip (percutaneous MV repair) for 2ry MR in CCF improves hospitalization rates -

ICD

MADIT-II

Ischemic CMpathy : MI 1m or earlier, EF < 30%, NYHA ≤ III
Improves mortality – NNT 18
Criticism – 20% developed worsening HF

SCD-HeFT

ICD Vs amiodarone Vs placebo
Ischemic or non ischaemic CMpathy, NYHA I-III, EF < 35%
Improves mortality. No mortality benefit with amiodarone

MIRACLE

CRT improves HF symptoms and function in EF < 35% QRS > 130

CARE HF

CRT improves mortality in EF < 35% NYHA III/IV QRS > 130

MADIT-CRT

CRT-D Vs ICD in EF < 30%, NYHA III/IV, QRS > 130s
CRT-D improves mortality

Fe therapy

IV ferric carboxymaltose weekly for Fe deficiency (ferritin < 100 or 100-200 with Tr sat <20%) (with or without anemia: Hb 9-13-5) for HFrEF (< 40-45%)
Improves symptoms and functional capacity – FAIR-HF (24 wk FU) (2009)
Improves symptoms, functional capacity and hopsiltazaitons for HF – CONFIRM HF (52 wk FU) (2014)

CASTLE AF

Dyslipidemia

	Primary prevention	Secondary prevention
Statin	JUPITER, WOSCOPS	4S, LIPID, HPS, CARE, MIRACL, SPARCL High > mod : PROVE IT TIMI 22, TNT
Ezetimibe	-	IMPROVE -IT
PCSK9i		ODYSSEY OUTCOME FOURIER

other	Helsinki Heart Study - gemfibrozil	FIELD, REDUCE-IT

Statin trials

WOSCOPS **NEJM 1995**

7000 men with LDLC > 155 without CVD
FU 5y
Pravastatin 20mg vs placebo
Reduces CV events and CV mortality

JUPITER **NEJM 2008**

Rosuvastatin reduces CV events in older adults with high hsCRP in primary prevention

Inclusion:
- Men > 50y, women > 60y, high hsCRP

Exclusion:
- DM, DL (LDL > 130, TG > 500), previous ASCVD, inflammatory disorders

Population:
- 17 000, ~ 66y, 40% had Met Xd

Intervention:
- Rosuvastatin 20mg vs placebo 5y – truncated at 2y (and values estimated)

Findings :
- Reduces LDLC by 50%
- Reduces CV events at 5y – NNT 25
- Reduces all cause mortality. CV mortality not reported
- Increases new onset DM – NNH 260 at 4y
- No increase in muscle injury

Limitations :
- Control group had more hypertensives and had a lower aspirin use
- Not compared with normal hsCRP people, so hsCRP as a decision determinant not confirmed
- Asians not included – different rosuvastatin metabolism
- Industry sponsored

Primary prevention in older adults > 75y

Meta analysis from many statin trials, by Cholesterol Trialist collabartation published in 2019 Feb showed no benefit. But pt population was small. Large RCT is underway – STAREE – await results in 2022

MIRACL **JAMA 2001**

Early atorvastatin post UA/NSTEMI reduces CV events in 2ry prevention

Inclusion
- UA/NSTEMI

Exclusion
- Dyslipidemia, T1DM, NYHA IIIB-IV

Population
- 3000, 65y, 65% men, DM 22%, HTN 55%

Intervention

Atorvastatin 80mg/d vs placebo, starting within 96h of hospitalization, 16 week FU

Findings

Reduced composite of all cause mortality, non fatal MI, cardiac arrest, rehospitalization for re ACS (last was the greatest contributor). NNT = 38
LDLC reduced by 50% (120 □ 60)

Limitations

STEMI and NSTEMI s Rx with PCI excluded
Safety of > 16 week use not tested
Underpowered to assess individual components of the composite end point

SPARCL NEJM 2006

Post stroke / TIA atorvastatin 80mg/d (Vs placebo) at 5y FU reduces recurrent stroke/TIA
4700
Industry sponsored
Underpowered for mortality assessment
Suggestion of increased ICH (disproved later)

EBM for statins in DM

- **CARDS – primary prevention in T2DM**
- Subgroup analysis from 4S
- HPS – DM subgroup
- CARE – pravastatin post MI in DM/IGT patients
- TNT – treating to new targets, 10 000 stable CAD (15% DM+). Atorva 80mg vs 10 mg aiming LDLC 75 and 100 (achieved same). Better mortality reduction
- ASCOT-LLA
- ASPEN
- Reviews / meta analysis by CTT

CARDS

2400 T2DM without dyslipidemia and ASCVD
Atorva 10mg vs placebo
3.9y FU
Reduced ACS + revascularization + stroke by 37%

CTT (Cholesterol Treatment Trialists) Meta analysis from CARDS and subgroups of DM+ from ALLHAT-LLT, ASCOT-LLA, HPS etc:
Reduction of LDLC by 1 mmol/L reduces
major CVE by 21%
CV mortality by 13%
All cuase mortality by 9%

4S

Simvas reduced all cause mortality and CV mortality in people with ASCVD
4444

High intensity statin

PROVE IT TIMI 22

Ator 80 prava 40 post ACS
2y FU
Reduce CV death and events

TNT

atorva 80 Vs 10 in people with stable CAD and hyperlipidemia
80 reduces CVD but not mortality alone

Ezetimibe

IMRPOVE-IT **NEJM 2015**

Ezetimibe when added to moderate intensity statin, reduces composite of CV death and non fatal CV events in post ACS patients

Inclusions

> 50y, ACS within last 10 days (or high risk UA)

Exclusions

Recent stroke/TIA
Unstable pt

Population

18 000, 66y, M 75%

Intervention

Simvastatin 40mg + ezetimibe 10mg / day Vs simvastatin 40 mg + placebo
6y FU

Findings

Improved primary composite – NNT 50
24% additional LDLC reduction

Limitation

Moderate intensity statin in control group
Small effect size (ARR 2%)
42% drug discontinuation rate! (equal in both groups)
Excluded stroke / TIA

ENHANCE

Ezetimibe Reduces LDL but not plaque size

CORONA

PCSK9i – proprotein convertase subtilisin kexin 9 inhibitor

Reduces LDLC by 60% when added to mod – high intensity statins

OSLER - evolocumab

ODYSSEY LONGTERM – alirocumab

Trialled for SECONDARY PREVENTION

~ 20k, ASCVD+ (~40% with DM), on statin with LDLC ~ 90, 2.5y FU, 54% LDLC reduction, 1.5% reduction in CV events, no mortality reduction

FOURIER **NEJM 2017**

25 000, 26m

ASCVD+ (80% - MI) with LDL > 70

63y, HT in 80%, DM in 40%, LDLC 90 □ 40 (54% reduction)

Evolocumab 2weekly or monthly SC + statin (mod-high) Vs statin (mod-high)

CV events (5 point MACE) – Absolute reduction 1.5%. NNT 74. NO MORTALITY REDUCTION

LDLC 90 □ 40 (54% reduction)

Limitation – low mortality rate in both groups – underpowered for mortality benefit assessment

ODYSSEY OUTCOME **NEJM 2018**

19 000, 2.8y

ASCVD+ (recent ACS) (DM 30%)

58y, LDLC 90 □ 66

Alirocumab (SC 2 weekly) + statin Vs stain

CV events reduced by 1.6% (4 point MACE) - NNT 63, NO MORTALITY REDUCTION

	FOURIER	ODYSSEY OUTCOMES
Population	Stable ASCVD	Recent ACS
Qualifying LDL-C, mg/dL	≥70	≥70
Primary endpoint	5-point MACE: CV death, MI, CVA, UA, coronary revasc.	4-point MACE: CHD death, MI, CVA, UA
Follow up	26 months	34 months
Age (median, years)	63	58
ACS <1 year	20%	100%
High-intensity statin	69%	89%
No statin	0.2%	2.5%

Fibrate

FIELD – Lancet 2005

10 000 T2DM 50-75y. not on statins

TC 3-6.5 (114 - 250), TG 1-5(88-440)

Fenofibrate 200mg od Vs placebo

Did not reduce coronary events (non fatal MI and coronary death)

Reduced cardiovascular events (2ry outcome – non fatal MI and revascularizations)

Increased pancreatitis and pulmonary embolism

Reduced need for laser Rx in DR independent of lipids (separate publications)

Limitation -

ACCORD-LIPID – no benefit in adding fibrate to simvastatin in reducing CVD events

ACCORD follow on (ACCORDION) – overall no benefit. CV reduction in people with TG > 204 and HDL < 34

n3 fatty acids

REDUCE-IT – NEJM 2018 Nov
Icosapent ethyl 2g bd added to statin vs statin alone for primary / secondary prevention
TG 150-500 people
Reduce TG by 40 mg/dL
Reduce CV events (MI and CV death: NNT 20). Reduced CV mortality (NNT 100)
Increased AF (NNH 100), bleeding (non-significant)
Limitations:

- Lesser benefit in primary prevention cohort
- Compared against mineral oil – proinflammatory
- Lower use of ezetimibe and PCSK9i
- CVE reduction did not parallel TG reduction. May have a TG independent effect
- Highly purified preparation – expensive (600 Rs/day)

*__ASCEND__: among DM w/o ASCVD, n3 FA 1g/d supps did not improve CV events
__VITAL__ – n3 1g/d in M > 50y or F > 55y did not reduce ASCVD or cancer (25000, 5y FU). Same study also showed vit D 2000 IU/d did not reduce cancer or ASCVD.
__REDUCE-IT__ : in pts with persistnet hyperTAG (135-499) despite statins (and LDL 40-100) and high CVDr (ASCVD+ / risk factors +), icosapent ethyl (n3) 2g bd reduce CV events

Stroke

2018 : DAWN, DEFUSE, POINT, WAKE-UP

NINDS
16% increase in functional favourable outcome
6% increase in bleeding

If you receive rtPA
Chance of significant improvement within 24h is 46% (increased by 20%)
Chance of functional independence at 90d (mRS 0-1) is 40% (increase by 50%)
Chance of ICH is 6%

ECASS-3
< 80y,
Placebo group – high rate of past stroke
Increased bleeding. NNT 14

WAKE UP
DWI FLAIR mismatch to determine stroke age
Alteplase
Improves functional outcome
Stopped premature due to cessation of funding

THALES

ENCHANTED 2/2019 Lancet

In pts with acute ischemic stroke Rx with Tlysis, aggressive BP reduction (aim 130-140) Vs standard control (180), starting within 6h and maintaining for 72h. N 2000+

Reduced ICH

No difference in mRS at 90d

Limitation, BP targets not met. Achieved levels were 144 Vs 150 – no major difference. Only mild to moderate strokes selected, bleeding risk higher with large strokes.

Time from LKW to Rx initiation	**< 3h**	**3-4.5 h**	**4.5 - 6h**	**6-16h**	**16-24h**
rtPA (3h: NINDS rtPA, ATLANTIS. 3 - 4.5h: ECASS-3)					
Inclusion	≥ 18y AIS NIHSS > 0	≥ 18y AIS NIHSS ≤ 25 ASPECT > 6	None	None	None
Exclusion	CIn for rtPA	Over 80y* DM AND Past stroke* > 1/3 of MCA OACs Other CIn for rtPA	-	-	-
TNK superior to rtPA in pts presenting within 4.5h, undergoing T'ectomy (EXTEND IA TNK – was the 1st trial to try TNK at 0.25 mg/kg. other trials at 0.4mg/kg failed to show superiority)					
WAKE UP T/lysis if MRI demonstrates stroke is < 4.5h (DWI +, but no hyperintensity in FLAIR) improves outcome. (stopped prematurely due to cessation of funding)					
Thrombectomy (MR CLEAN, ESCAPE, EXTEND IA, REVASCAT, SWIFT PRIME, THRACE)					
Inclusion	> 18y Pre morbid mRS 0-1 NIHSS ≥ 6 ASPECT ≥ 6 Can start within 6h of Sy onset ICA / M1 clot seen in CTA / MRA			-	-
Exclusion					
Delayed thrombectomy				**DEFUSE-3**	**DAWN**
	-			Core-perfusion mismatch	Core – clinical mismatch
Inclusions				**DEFUSE-3** 18-90y LKW 6-16h Basal mRS 0-2 NIHSS ≥ 6 ASPECT ≥ 6 Ischemic > 70mL, infarct < 15 mL, isch:infarct > 1.8 ICA/M1 clot	**DAWN** > 18y LKW 6-24h Basal mRS 0-1 NIHSS ≥ 10 ASPECT ≥ 6 Infarct volume < NIHSS ICA/M1 clot
Exclusion				Preg, BP, Glc, fits, Plt, INR Stroke > 1/3 of MCA	Preg, BP, Glc, fits, Plt, INR Stroke > 1/3 of MCA
Aspirin 160-300mg (IST, CAST) within 24-48h from stroke onset. Preferably 24h after t'lysis / t'ectomy					
SECONDARY PREVENTION					
Antiplatelets in atherosclerotic stroke (IC or EC cerebral vessels, aortic arch atheroma)					

Aspirin IST, CAST, many others in meta analysis. superior to warfarin in safety - **WASID**
Aspirin 25mg + dipyridamole 100mg bd equal to aspirin (**ESPS-1, ESPS-2, ESPRIT**)
Clopidogrel 75mg /d equal to aspirin **CAPRIE** and asp-dipyr **(PRoFESS)**
DAPT for 21d (CHANCE): aspirin 75mg/d x 21d + clopid 75mg/d x long term starting within 24h of Sy onset, first dose being 300mg each in: 1. Minor stroke (NIHSS ≤) 3 or high risk TIA (ABCD2 ≥ 4) 2. Premorbid mRS 0-1 3. Not candidate for rtPA **DAPT for 90d:** Reasonable (AHA/ASA 2014) – indirect data from **SAMMPRIS** (that showed stenting increase mortality Vs DAPT in IC 70-99% stenosis) Harmful after minor stroke/high risk TIA – **POINT**. More bleeds. Best stroke reduction in 1st few weeks. Bleeding risk throughout 90d. so DAPT for 1st few weeks will be beneficial
High intensity statin
Antiplatelets in non atherosclerotic stroke
AF, non RMVD VHD, PFO, thrombophilia – consider aspirin if cannot anticoagulate
Atrial fibrillation
Warfarin - **EAFT**, for 2ry Px, INR 3, NNT 12.5, 1y, Vs placebo. (1ry Px, meta analysis. NNT 33, 1y Vs placebo) Superior to antiplatelets (aspirin: **EAFT**, clopid: **ACTIVE-W**)
Apixaban **ARISTOTLE**. 15000, 5mg bd Vs warfarin (TTR 62%). Non inf design, crossed superiority margin (1.8y, any stroke or systemic embolism). 1ry Px = 2ry Px. Less ICH. Same GIB. Non valvular AF **AVERROES –** superior efficacy and equal safety to aspirin when warfarin was unsuitable
Dabigatran – **RE-LY** 150mg bd and 110mg bd were non inferior to warfarin and equally safe. 1ry Px? Non valvular AF
Rivaroxaban – **ROCKET-AF**. Riv 20mg/d non inferior to warfarin. Less ICH, less fatal bleeds, more GI bleeds. Among warfarins, TTR was 55% (other trials 65%). 1ry Px = 2ry Px efficacy. Non valvular AF
LAA occlusion – **PROTECT AF**: non inferior to warfarin
PFO closure is beneficial in < 60y, no/minimal cerebral vessel atherosclerosis, no other uncontrolled RF for stroke: **CLOSE, REDUCE, meta analysis of PC + CLOSURE + RESPECT short term.** Transient increase in AF periprocedure
CEA – NASCET, ECST : 70-99% stenosis – within 6m. 50-69% stenosis – do within 2 weeks

Antiplatelets for stroke prevention

Single antiplt

Aspirin Vs placebo	IST, CAST (1997)
Clopid Vs placebo	CAPRIE (stroke / CVD) (1996)
Dipyridamole Vs placebo	
Aspirin Vs clopid	
Aspirin Vs didyridamole	
Clopid Vs dipyridamole	

DAPT

Long term

Asp + clopd Vs asp	SPS3 (2012) After lacunar stroke, long term DAPT Vs clopid. FU
3.4y	
	Increase bleeding No benefit in stroke reduction
	CHARISMA (2006)

	DAPT for 1ry prevention of stroke (in pts with stable CAD or high CV risk) and 2ry Px of CAD DAPT – increase bleeding, no reduction in MACE, reduces stroke (NNT 200)
Asp + clopid Vs clopid	MATCH (2004) 2ry Px after stroke / TIA No reduction in recurrent stroke/TIA. Increased Bleeding Most were ***lacunar strokes*** – less likely to benefit from DAPT
Dipyridamole + aspirin > either alone	ESPS, ESPRIT
Dipyridamole + aspirin = clopidogrel alone	PROFESS Based on match asp + clopid converted to clopid Dipyrim -higher bleeding, and headache

Short term

CHANCE (2013)

- 5100 chinese
- Wthin 24h of minot stroke or high risk TIA
- Asp 75-300mg stat □ 75mg/d x 21d + clopid 300mg stat □ 75mg n for 90d Vs clopid 400 mg stat □ 75mg n for 90d + matched placebo
- Decrease recurrent stroke – NNT 29
- No increase in bleeding
- 300 clopid loading dose. DAPT for 21d, aspirin thereafter?
- Limitations -
    - Chinese – high rate of underRx of CV R/Fs, altered clopid metabolism, inherently high CVDr
    - Benefit after 90d not known

POINT (2018)

- 4900
- Within 12h from minor stroke (NIHSS $\leq$ 3) / high risk TIA (ABCD2 $\geq$ 4)
- Asp 50-325mg/d x 5d □ 75mg n + clopd 600 □ 75 n Vs aspirin 50-325 / d x 5d □ 75mg n + placebo for 90d
- Excluded – **candidates for T'lysis, people with AF, candidates for CEA**
- 1ry outcome – composite of stroke, MI, ischemic vascular death
- Decrease 1ry outcome : NNT 66, increase major bleeding NNH 200
- Limitation – stroke etiology not considered. Higher clopid loading dose than in CHANCE. 30% discontinuation rate

Combined analysis

Stroke reduction of DAPT is strongest in early few weeks. Bleeding risk is static throughout. So, benefit > risk window is the first few weeks for DAPT after minor stroke / high risk TIA

DOACs – see AF

CEA
ESCT within 6m

NASCET 1998
1st trial – benefit if occlusion > 70%
50-70% occlusion – still beneficial
within 6m

ESCT
Within 6m of stroke
Benefit only if occlusion > 80%

Acute BP reduction
Safe. But no benefit in mortality / functional outcome – multiple RCTs, and meta analysis
Most recent RCT - ENCHANTED

ICH BP targets
INTERACT-2: Rapid BP reduction (< 140 within 1h Vs < 180) in ICH did not improve 90d functional outcome or death. Vairety of antiHTN used – their individual influences not known

ATACH-2: 110-140 Vs 140-180 no difference (achieved SBPs: 129 Vs 141) in functional outcome or mortality. Insignificant reduction in hematoma expansion

PFO closure
< 60y, PFO, cryptogenic stroke. Embolic stroke on imaging Fx in later studies. TOE for R-L shunt
Higher risk – large PFO, LL DVT, PFO aneurysm, L-R shunt

CLOSURE – no benefit
Device related complications, out of market
6m DAPT aspirin
Medical group aspirin or warfarin
Increased AF

RESPECT, REDUCE, CLOSE – beneficial

Meta analysis excluding CLOSURE – benefit+. NNT 30

AVERT
Aggressive rehab within 24h – sitting standing walking
Less favourable

CADISS

Carotid or vertebral dissection – antiplt = anticoag (3m Rx. Beyond this at [hyscician discretion) – no difference in rate of recurrene or recanalization

Nutrition

***ASCEND**: among DM w/o ASCVD, n3 FA 1g/d supps did not improve CV events
VITAL – n3 1g/d in M > 50y or F > 55y did not reduce ASCVD or cancer (25000, 5y FU). Same study also showed vit D 2000 IU/d did not reduce cancer or ASCVD.
REDUCE-IT : in pts with persistnet hyperTAG (135-499) despite statins (and LDL 40-100) and high CVDr (ASCVD+ / risk factors +), icosapent ethyl (n3) 2g bd reduce CV events

High fibre (25-29g/d) and high whole grain reduce
T2DM, CAD, CRCA and mortality – meta analysis in Lancet

PURE
Prospective Urban and Rural Epidemiology study
Target 225 000. To study impact of urbanization, diet, and lifestyle on mortality

- High fat decreases mortality (~30-40% of calorie, including Sat fats)
- Low sat fats (< 6% as rec by AHA) are harmful!
- Fruit / veg / legumes 3-4 servings a day decreases mortality (traditional rec – 5 servings)
- High CHO increases mortality
- None of above 3 (CHO, fat, fruit-veg-legume) are associated with change in CV events
- Dairy intake (> 2 servings a day Vs none) decrease mortality and CV events
- Higher physical activity decrease mortality and CVEs
- Same findings in Asian and non Asian countries
- High lipids – high LDL, high HDL, low TG – low TC:HDL
- High CHO – low LDL, low HDL, high TG – high TC:HDL
- ApoA : ApoB ratio as the best lipid marker of CV prediction
- Bidi increase cardiorespiratory disease and mortality

Limitations
Recall bias – food frequency questionnaire
High sat fat source (meat) would have provided life saving micro-nutrients
Observational design
Marked dietary and cultural variations pooled together

COPD

LAMA > LABA for exac reduction		POET COPD (tiot > sal), INVIGORATE (tio > indac) ((hence LAMA id 1st line in group C) (inclusions in both fit to group C / D)
LAMA/LABA > LABA/ICS	:	FLAME (& Cochrane review of 11 studies)
Adding LAMA to LABA/ICS	:	FULFIL, TRILOGY
Adding ICS to LABA/LAMA	:	TRIBUTE, IMPACT
Sy+ with triple Rx	:	Roflumilast (REACT, ACROSS) Azithromycin 500mg 3 times a week (COLUMBUS – 92 pts 3 or more exac last yr)
Triple □ double safe in infreq exac	:	SUNSET

Beta blockers vs other antiHTN in non COPD pts on long term fu
BB reduced risk of COPD admissions and COPD related death.
Retrospective study from Danish prescription registry. Limitations
1. Those with COPD probably were not prescribed BB at the outset
2. Those who got the COPD / btomcjospasms ppt by BB would have had BB discontinued.
3. Those she received BB would have had heart disease as well. Reduced admissions may reflect cardiac admission which are easily confused with COPD
4. Those who were prescribed might not have been compliant due to SE
POSTULATED MWCHANISM
Chronic BB upregulate bronchial beta receptors. BB reduce infl and mucus secretion

Bronchiectasis

EMBRACE	Azithro 500mg 3/wk decrease exac (1/more exac last yr)
BAT	Azithro 250mg daily decrease exac and improve PFT (3/more exac last yr) resistance rate :24% 88%
BLESS	Erythro 400mg bd decrease exac (2/more exac last yr)

Meta analysis : macrolides reduce exacerbations, retard progress of PFT and improve SGRQ

IPF / ILD

Pirfenidone for IPF improves mortality – ASCEND, CAPACITY
Nintedanib improves LFT and exercise in IPF – TOMORROW, INPULSIS
Nitendanib + sildenafil is of no benefit – INSTAGE
SSCl-ILD

- SLS -1 : CPM po > placebo
- SLS – 2 :MMF 3g/d = CPM in efficacy better in safety
- SLS-3 : MMF Vs MMF+Pirfenidone

CAPACITY - 2011
2 trials
72 wks or more FU
801mg tds Vs 399mg tds Vs placebo
Decrease PFT decline
801mg tds decreases mortality

ASCEND – 2013
Pirfenidone 801mg tds- TGFβ/TNFα modulator Vs placebo
IPF Dx within 2y, Baseline FVC – 68%, DLCO 44%
Decrease progression free survival and FVC decline
No decrease in mortality
SE – photosensitivity, dizziness, vomiting

TOMORROW

INPULSIS
Nintedanib – Tki, block actions of FGF PDGF, VEGF
Decrease FVC decline
Underpowered for mortality assessment

SLE

Lupus nephritis
Novel agents

GCA

AAV
- RAVE
- MAINRITSAN

AS

PsA

IBD

Exlcusive enteral nutrition (poor palatability) Vs individualized food based diet – had same effect on gut microbiome and gut inflammation

Anaerobically prepared pooled donor FMT offered superior remission over autologous FMT for mild to moderate UC

NAFLD

Cirrhosis

IBD

FMT + vanco is superior to vanco or fidoxamicin in recurrent C diff PMC (N = 64 RCT) in achieving clinical and microbiological remission (Hvas et al gastroenterology 2019)

Sepsis

- Crystalloids. No added benefit with albumin (SAFE – albumin vs saline for hypovolemia in ICU, CRYSTAL – colloids were not better than crystalloids for hypovol shock in ICU pts – most had sepsis. ALBIOS – maintenance albumin for septic pts to keep alb > 30 Vs placebo on 28d mortality)
- Intotropes – NA, vaso, Adr
- Steroids
  - HC alone not effective : ADRENAL
  - HC 50mg 6h + flud 50mcg NG od reduces mortality : APROCCHSS
- HCO3 if pH < 7.2 reduce RRT need at 30d : BICAR-ICU
- CBS 140-180 : NICE SUGAR
- ARDS: Lung protective ventilation : TV 6mL/kg, max plateau 30, higher PEEP, prone
- PPI
- DVT Px – GCS, pneumatic compression, LMWH if not CIn
- Hb 7 (TRISS), plt 20 (50 if bleeding)
- RRT if In
- HCO3 if pH < 7.15

Steroids in septic shock

	French	Corticus	Hypress	ADRENAL	APROCCHSS
Year	2002	2008	2016	2018	
N	300	400	400	4000	
Dosing	50mg 6h IV 7d + FC	Bolus	Bolus or infusion	Infusion 200mg/d	
Shock reversal	Yes	Yes	Yes	Yes	
Mortality	Reduce 28d mortality	No benefit	No benefit	90d no benefit	
	HC given only to ACTH non responsive pts			Shorter ventilation Reduce BT need Shorter ICU stay	
	Single centre, small N				

Goal directed therapy

	EGDT (Rivers et al)	ARISE	PROCESS	PROMISE	Zambian study
	2001	2014	2014	2015	
	260	1600	1300	1200	
	CVP, MAP, ScvO2	EGDT Vs usual care	Usual care Vs EGDT Vs novel protocol (non-invasive monitoring)	EGDT Vs stanard care	
	Reduce mortality	No reduction in 90d mortality	No difference in mortality	No difference in mortality More expensive	Increase mortality
	Unblinded Major contributor not assessed BT protocol not clear – may have confounded	Unblinded Not very ill pts Usual care also met EGDT	EGDT needed more vasopressors and usual care needed more fluids		high HIV, high Fluid & dopamine, vital measurements sub-standard

ANDROMEDA-SHOCK – JAMA 2019/feb

Septic shock treatment targeting peripheral perfusion correction (CRFT) Vs normalization of lactate.
28d mortliality - Insignificant reduction
qSOFA improvement – significant improvement

Blood transfusion

	TRICC	**TRISS**
	1999	2014
	838	Very restricted inclusion exclusion so only 13% participate!
	Critically ill normovolaemic, low Hb, without overt bleeding	Hypovolaemic anaemic septic shcok
	Hb 7 vs 10 (restrictive vs liberal)	Hb 7 vs 9
	Restrictive – mortality reduced	Equal 90d mortality
	Compatible with UGIB study	

NICE SUGAR
MICU and SICU patients
140-180 Vs 81-108
Former caused less deaths

Critical care

Balanced crystalloids better than saline – SALT-ED, SMART (note: NS preferred in cerebral edema)
Septic shock – HC alone not useful for mortality (but shorten ventialiton and ICU stay)– ADRENAL, HC + FC useful – APROCCHSS
Meta analysis of 37 RCTs – steroids in sepsis improve 28d mortality, inotrope requirement and ICU stay

HCO3 infusion reduces RRT need – BICAR-ICU
Haloperidol for Px of delirium in ICU no benefit : REDUCE
Halo / ziprasidone to Rx delirium in ICU no benefit : MIND-USA
So consider for agitated delirium only for shortest possible duration.
In AKI, early RRT over late RRT
Improves outcome : ELAIN (mostly Sx pts, HD offered at AKIN-2) (2016)
Does not improve outcome : AKIKI (MICU, HD from AKIN-3 2016), pooled analysis from ELAIN & AKIKI
Does not improve outcome in general or in people with sepsis / ARDS / shock : IDEAL-ICU
PPI pantaprazole Vs placebo – small reduction in GI bleeding, no mortality difference

PCKD

Tolvaptan –
Slows kidney volume growth and GFR decline in early PCKD (GFR > 60) : TEMPO
Slows GFR decline in advanced PCKD (GF 25-65) : REPRISE
Reversible hepatotoxicity was a concern

FEATHER
Febuxostat did not retard GFR decline compared to placebo in CKD-III
443pt 2y FU

NAC for prevention of contrast nephropathy – no use (IV/PO) (and NaHCO3 also no use) - PRESERVE

Migraine

CGRP monoclonal Ab monthly SC galcanezumab

Toxicology

RV -

HNV – prednisolone

Krait bite dose

Oral Vs IV NAC vs methionine

Sita Vs glimepiride for ASCVD – prof SL

Zn

Stroke head positioning

GAMES-RP

IV glyburide reduce cereral edema, midline shift and death in malignant MCA infarcts – 75pt study

REACH – hydroxyurea in African children with SCA

Reduced vaso-occlusive crisis and prolonged survival (by icnreaseing HbF)
Reduced malaria by 50% (HbF has protective effect on malaria)

Research papers in 2018

NEJM

HERCULES – capalicizumab for TTP *(anti vWF Ab) – faster plt rise, lower composite of thrombotic events, recurrence and mortality*

Conservative transfusion strategy *to limit BT to Hb 7-10 moderate anemia in hospitalized pts improved outcome in an observational study*

DAWN *– thrombectomy 6-24h (jan 4) : 50% achieve indepecndece Vs 15% in control group. (same in DEFUSE)*

CASTLE AF *– catheter ablation in AF with CCF imporves outcomes. N Engl J Med 2018; 378:417-427*

PRESERVE – IV NaHCO3 or IV NAC gives no benefit over NS or placebo in preventing AKI in angiogram in high risk patients. N Engl J Med 2018; 378:603-614

Edoxaban reduces DVT but increases bleeding compared to daltaparin. N Engl J Med 2018; 378:615-624

DEFUSE 3 *– thrombectomy 6-16h beneficial N Engl J Med 2018; 378:708-718*

ADRENAL *– hydrocortisone does not improve mortality at 1-3m in patients ventilated with septic shock, but shortened ventilator and ICU stay N Engl J Med 2018; 378:797-808*

APROCCHSS *– hydrocortisone (IV 50 mg 6h) +fludracortisone (50micg od NG) improves 90d mortality in septic shock patients in ICU (SOFA 3 or 4) when started within 24h*

SALT-ED *– balanced crystalloids decreased adverse renal outcomes over saline a 1m in non critically ill patients N Engl J Med 2018; 378:819-828*

SMART *– balanced crystalloids (ringer lactate, Plasma Lyte A) improve composite renal outcomes (mortality at 30d, need for new RRT, and worsening renal impairment) over normal saline in critically ill patients. ARR: 1% N Engl J Med 2018; 378:829-839*

Quadrupling the ICS dose reduces asthma exacerbations - N Engl J Med 2018; 378:902-910

***CARES** – febuxostat is equal to allopurinol in CV events in at risk people, but had higher CV death and all cuase death rate N Engl J Med 2018; 378:1200-1210*

Gene therapy for beta thal major using a lentivrus to deliver a beta glob gene (A-T87Q) minimized or eliminated the transfusion need N Engl J Med 2018; 378:1479-1493

***EXTEND IA TNK** – TNK (0.25mg/kg, max 25mg) is better than alteplase (0.9 mg/kg max 90mg) for reperfusion (> 50% patency and absence of retrievable clot at angiogram) and 90d outcome (mRS) in patients with stroke presenting within 4.5h and undergoing thrombectomy. N Engl J Med 2018; 378:1573-1582 (TNK is more fibirin specific, and has a longer duration of action)*

***IMPACT** – fluticasone-vilanterol-umeclinidium combo reduces exacerbations better than fluti-vilan or vilan-umecli. But caused more pneumonia. N Engl J Med 2018; 378:1671-168*

***SYGMA 1** – budesonide+formeterol SOS causes less exacerbations and symptoms than terbutaline in mild asthma. Regular budesonide gave an even better outcome but increased he steroid exposure. N Engl J Med 2018; 378:1865-1876*

***SYGMA -2** – budesonide + formeterol gave non inferior exacerbation rate to budesonide bd, caused less steroid exposure but symptom control was poorer. N Engl J Med 2018; 378:1877-1887*

***NAVIGATE ESUS** – rivaroxaban 15mg od was not superior to aspirin 100mg od in preventing recurrent stroke after embolic stroke from unknown source, but increased bleeding N Engl J Med 2018; 378:2191-2201*

***BEZURSO** – Bezafibrate 400mg od (PPAR agonist) as an add on significantly improve **biochemical response** in those with PBC not responding to UDCA monotherapy N Engl J Med 2018; 378:2171-2181*

***PECARN DKA FLUID** – NaCl content or rate of administration did not change neurological outcome in pediatric DKA N Engl J Med 2018; 378:2275-2287*

***POINT** – after minor stroke or high risk TIA, giving asp + clopid for 90d caused less re infarcts but increased hemorrhage significantly compared to aspirin alone. Protection was best in first few weeks, bleeding was throughout.*

***DENGUE VACCINE** – tetravalent dengue vaccine (CYD-TDV) in children 2-16y of age decreases hospitalization and incidence of severe DF for 5y in seropositive children but increases both risks in seronegative. (dengue sero status as assessed by NS1 Ab IgG - ELISA) : in a post hoc case control analysis*

	CYD14 (2014)	CYD15 (2015)	Phase 2b trial (2012)
Region	SE Asia	Latin America	Thailand
Age group	2-14y	9-16y	4-11y
Vaccine & protocol	CYD TDV, 0,6,12	CYD TDV, 0,6,12	Tetravalent 0,6,12
End point	VCD at 25m F/U	VCD 25m F/U	VCD 25m F/U
Vaccine efficacy	56.5%	60.8% Serotype 1: 50.3% **Serotype 2: 42.3%** Serotype 3: 74% Serotype 4: 77.7%	30.2%

APeX1 *– once daily oral kallikrein inhibitor reduces angioedema frequency and improves QoL.*

Treatment of latent TB

4 months of rifampicin is not inferior to 9m of INAH in the treatment of latent TB. Former offers better safety.
F/U was for ~ 28m including Rx period
INAH 5mg/kg – max 300 mg, Rifampicin 10mg/kg max 600mg

REVEAL: *anicetrapib added to atorva in pts with CVDr, reduces LDLC (from 61 to 53), increases HDLC (40 to 85), and reduces ASCVD events (11.8 Vs 10.8%, RR 0.91, NNT 100) compared to placebo. Anicetrapib is a CETP inhibitor*

WAKE-UP : *for wake up strokes of unknown time duration, where pt is not a candidate for thrombectomy, and MRI DWI and FLAIR is compatible with a stroke of < 4.5h (DWI positive, FLAIR negative), rtPA improves 90d functional outcome significantly. Insignificant increase in bleeding was noted. Trial was prematurely stopped due to cessation of funding and it is uncertain whether had the full trial being done, bleeding would become significantly higher.*

COMMANDOR-HF*: rivaroxaban 2.5mg/d for HF (EF < 40%) without AF does not improve 3 point MACE. Hypothesized due to the observation that CCF activates clotting mechanisms*

Three trials proved aspirin is not useful for primary prevention of CVD

ASCEND trials. Median FU 7y, 15 000

Aspirin *100mg/d for primary prevention of ASCVD in DM*
Improves MI / stroke / CV death: NNT = 100
Increases major bleeding: NNH = 100 !!

ARRIVE lancet 2018 Aug, 12 000

Aspirin 100mg/d for primary prevention of ASCVD in non DM mod risk pts (M > 55y, W > 60y)
Median FU – 5y
No benefit in reducing ASCVD events over placebo. Adverse effects are also comparable.
Benefit may not have been seen due to low event rate, which is probably due to institution of good preventive care overall

ASPREE *- NEJM, 19 000*
AUS and US
Community dwelling > 70y w/o CVD / dementia / disability
Aspirin 100mg od vs placebo
Terminated at 4.7y due to lack of benefit
In elderly (> 70y) aspirin doesn't reduce CVD / disability free survival but increase bleeding and cancer related deaths

All three studies reported lower event rates than expected – reflecting improved CVD care (better lipid, BP and DM Rx)

Omega 3 FA *1000 mg/d does not improve ASCVD outcomes in primary prevention in DM*

Oral antibiotics for IE

Study from Denmark
400, ~ 64 years.
Left heart IE (native / prosthetic / device) caused by strep / staph / CNS / enterococci
After at least 10d of IV abtcs / 7d after Sx, still needing at least 10d of Abtcs, stable, not in need of Sx / afebrile at randomization
Randomized to receive IV Vs oral at home
Reviewed 2-3 d / week until completion. TEE on or before completion. Reviews at 1wk, 1,2,6 months
Oral antibiotic decided based on ABST and MIC. Absorption confirmed by drug level monitoring after 1st dose
Oral Abtc for completion is non inferior to IV completion in this cohort of patients. No different in subgroups
Limitations
- *Left heart only*
- *Selected organisms only*
- *Strict exclusion / inclusion criteria*
- *Strict follow up- not always feasible practically*

Zoledronate for osteopeaenia – NEJM 20/12/2018

New Zealand
MCRCT
IV Zoledronate 18 monthly *Vs saline as placebo*
> 65y, women T -1 to -2.5 at hip / femur neck, N > 2000
6y FU
Reduced vertebral and non vertebral fragility #: ***NNT 15***
No difference in adverse effects, slight benefit on CV disease and cancer – but underpowered for accurate assessment

LANCET

TRED-HF

Discontinuing Rx after Sy resolution and EF normalization in DCM lead to relapse in 45%. So need contd Rx until better markers of remission are identified

Meta analysis of SGLT2i

- Reduce ASCVD events by 11% in 2ry Px but not in 1ry Px setting
- Reduce CV death and HF hospitalziaiton by 23% in 1ry and 2ry Px
- Reduce CKD progression by 45% in 1ry and 2ry Px setting

CAMELLIA-TIMI-61 : locarserin prevents development of DM, induce normoglycemia in people with DM and reduces microvascular complications of DM
N 12000, FU 3.3y. > 40y, BMI > 27

BICAR-ICU : critically ill patients in ICU with pH < 7.20 and HCO3 < 20 and pCO2 < 45 were given IV 4.2% NaHCO3 infusion (max 1L a day) starting within 48h of ICU admission. In a multivariate analysis, this intervention reduced RRT need at 28 days, sp in those with AKI. Survival benefit was seen in AKIN 2 & 3 AKI pts.

STAMP : Rapid screening with **urine LAM** (lipoarabinomannan) **and Xpert MTB** improves diagnosis of **TB in HIV**. 56 day mortality benefit is seen in subgroups with CD4 < 100, severe anemia and clinical suspicion of TB. An RCT from Africa

AspECT: Aspirin and high dose esomoprazole reduce progression to adenoCA / high grade dysplasia in Barrett esophagus

Alcohol safe limits

Derived from Global Burden of Diseases – Alcohol collaborators
< 50y, major causes of alcohol related deaths – TB, RTA, suicide
>50y, major alcohol related CoD – cancer
Safe limit to prevent mortality -zero

ANSWER – long term Albumin for ascites

- OPEN label RCT
- Cirrhosis with uncomplicated ascites, on spiro > 200mg/d and fruse > 25mg/d
- SMT Vs SMT + HA
- HA : 20% human albumin in 50 mL vials : 40g twice a week x 2 wk once a week
- Med FU 18m, N = 431
- Benefits
    - Reduce mortality (NNT ~ 5.9)
    - Reduce SBP, HRS, hypoNa, hyperK, hep enceph
    - No reduction in UGIB
- Limitations
    - Open label design
    - HA pts had weekly health care contacts - ? better health care overall
    - Cost

TICH 2

Tranexamic acid for spontaneous ICH

- Reduced deaths at day 7 (not the primary outcome)
- No reduction in 90d deaths or functional outcome improvement

IOTA meta analysis (Improving Oxygen Therapy in Acute illness) Lancet 2018 April

25 RCTs

Liberal oxygen to keep SpO2 > 94-96% increases mortality without any advantage on morbidity

DiRECT

Intensive LSM (low calorie diet, exercise) lead to remission of diabetes in obese T2 diabetic people in an open label RCT with 306 participants

COMPASS

25000 pts with stable IHD (MI, st angina, PCI, CABG)
Riva (2.5mg bd)+Asp(100mg od) Vs Riva 5mg bd Vs Asp 100mg od
CV death/MI/stroke : RA > R = A (NNT = 50). Also reduced limb ischemic events
Major bleeding RA > R > A but RA didn't increase fatal or critical bleeds (NNH 100)

JAMA

PReVENT
In the absence of ARDS, low TV Vs IM TV ventilation has no difference in outcomes

The 'AI Clinician' –
to decide inotropes for ICU patients in sepsis
based on 17 000 sepsis pts data
A physician asst and not a substitution
Allows a personalized decision than a blanket decision for an average pt as in guidelines
Proven to improve survival in prospective studies

J DAVID – alfacalcidol for ESKDs on HD without 2ry hyperPTH gave no CV benefit

EsDEPACS – escitalopram for post MI depression within 3m (5-20 mg/day) reduces CV MACE at mean F/U of 8y N=300,
RCT from south Korea

Meta analysis of FOURIER, IMPROVE IT and REVEAL, shows that reduction of LDL from 70 to 21 reduces CVD events (RRR 0.78 for each 1 mmol/L drop in LDLC) is sustained without increase in myositis, hepatitis, cancer. It is similar to the reduction in CVDr when LDLC is lowered from 130 to 70 mg/dL

MERINO
Pip taz 4.5g 6h, was inferior to meropenem 1g tds in reducing 30 d mortality in patients with ESBL E coli or Klebsillea sepsis, despite being pip tazo susceptible in vitro
Although by definition, tazobactum should inhibit the beta lactamase of ESBLs, it seems clinical effects are inferior

TRIUMPH
od FDC – (telmisartan 20mg, amlodipine 2.5mg, chlothalidone 12.5 mg) was superior to standard care in pts with HTN requiring therapy anew or therapy escalation while on Monotherapy, in achieving BP target by 6m (67% vs 44%. 8.7 Vs 4.5 mmHg)
limitations – open label design. Exclusion of CKD. Small sample size. Short FU. CVD outcome not tested. Method of BP measurement

PIONEER 1 : underway – oral semaglutide for T2DM

APPROPRIATE
Propranolol crosses BBB – is there a central antiHTN effect?

Cobra

Cochrane review

CLINICAL QUESTION Among patients at high risk for or with established cardiovascular disease (ie, history of peripheral artery disease, stroke, or coronary artery disease without a coronary stent), is the addition of clopidogrel to aspirin associated with lower risk of mortality and cardiovascular events compared with aspirin alone?

BOTTOM LINE Clopidogrel plus aspirin is associated with a reduced risk for myocardial infarction and ischemic stroke and an increased risk for major bleeding compared with aspirin alone among patients at high risk for or with an established cardiovascular disease but without a coronary stent. However, combined therapy is not associated with lower mortality.

Andexanet – recombinant fXa which binds as a decoy to fXa inhibitors (apix, reiva, edox, betrixaban, eonx, fonda) and reduce anti Xa activity. Approved for apix and rivarox

Idarucizumab – dabi antidote

Normal aPTT and TT indicates dabi levels are insignificant
Normal anti Xa activity indicates anti X levels are insignificant. Normal PT aPTT in this setting is of no use

Warfarin	IV Vit K 5-10 mg + 4 factor PCC
Dabi	idarucizumab or 4F PCC / aPCC
Api / riva	andexanet or 4f PCC / aPCC
Edo / betrixa	4fPCC / aPCC

PRISMS
Alteplase, compared to aspirin, offers no benefit in treating minor non disabling stroke (NIHSS < 5) in terms of 90d mRS measured functional outcome. Insignificant increase in symptomatic ICH noted. Diffisuclt to interpret since study was prematurely stopped (N = 300, targeted N > 900)

VERTIS trials
Ertugliflozin – 4th SGLT2i
Alone (VERTIS MONO – A1c reduction ~ 1%), or in combo (VERTIS MET, VERTIS SITA, VERTIS SU)
Not beneficial in VERTIS – RENAL : CKD 3 patients

SAILORS
qSOFA (quick SOFA) is a better predictor of mortaility in hospitalzied patients with infection in low-middle income countries, over SIRS criteria
analysis from prospective studies in 9 LMICs, including SL

Fremanezumab – monoclonal Ab against calcitonin gene related peptide (CGRP) as monthly SC injection reduces migraine days by 1.3-1.5 per month compared to placebo. Comparison with other preventers to be done!

Vasopressin for distributive shock meta analysis – catechs + vaso causes less AF compared to catech alone. Variable effects on mortality, stroke, length of stay (2ry outcomes)

Insulin Vs Glyburide (glibenclamide) for GDM

Titrated insulin Vs glyburide (2.5mg – 20mg) – latter could not show non inferiority in efficacy. Caused nore neonatal hypoglycemia. Glyb administration aspects not described (should be at least 4h before meal. Further, pregancny has a high clearance rate of glyb so higher doses might have been effective)

LDL lowering efficacy with baseline LDLC level: meta analysis and meta regression

High intensity therapy achieved only in patients with a baseline LDLC > 100

WOSCOPS, 4S statins reduce LDLC when baseline is > 190
Further studies – higher intensity was better than lower intensity
Benefit proportionate to LDLC redcution – concluded Cholesterol Treatment Trialists (CT)

- 1 mmol/L reduction 22% relative reduction in vacular events, 20% relative redcion in coronart death

IMPROVE IT (ezetimibe), FOURIER (evolocumab) : added to statin, further reduces LDLC, and vascular events, but failed to show CV mortality

This meta analysis explains this observation. Mortality benefit appears only if the baseline LDL is > 100, proving CTT wrong
But, needs to be interpreted with caution due to confounding factors and ecological fallacy
Ecological fallacy – meta analysis compared trials at trial level rather than individual level. Which could give a wrong message if the participant characteristics were different
Confoudners – changes in general care over time, affects outcome in old vs new trials
Titrations, targets, follow up times were different

SMART (single Maintenance and Reliever Therapy)

ICS + LABA combined inhaler as reliever and preventer causes less exacerbations compared to ICS (+/- LABA) as preventer and SABA as reliever in adults with persistent asthma – meta analysis

LAMA for asthma – meta analysis

LAMA as add on to ICS

- Superior to placebo
- Not superior to LABA

LAMA LABA ICS had no added benefit over LABA+ICS

SECURE PCI : Statin loading in PCI

Brazil, multicenter RCT, N ~ 4500
Atorvastatin 80mg, 2 doses 24 apart, peri PCI for STEMI
Did not reduce 30d MACE in the total population
But in the 75% who received revascularization, MACE was reduced. Post hoc data limits validity
Conclusion: in high risk pt, early loading is probably beneficial

Lesinurad

Urate transporter-1
Decreases uric acid level in gout pts failing on allopurinol Monotherapy
No decrease in flares
Expensive, nephrotoxic
Increasing allopurinol or adding indomethacin would be a better choice!!

Tai ji quan (a tai chi based exercise) reduced falls in > 70y people than multimodal exercise (balance, aerobic, strength and flexibility) – JAMA 2018/dec

Revefenacin – first nebulized once daily LAMA for COPD maintenance therapy approved by FDA

BMJ

DPP4i increase IBD risk when used to treat T2DM – population cohort study:
Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study
BMJ 2018; 360 doi: https://doi.org/10.1136/bmj.k872

Patients with resolved AF have higher risk of TIA and stroke than those who had no AF, even without documented recurrence of AF
Retrospective cohort studies. May 18, 2018

SGLT2i increase risk of amputation and DKA compared to GLP1RA – observational cohort study from Denmark and Sweden.

2019

- FQ increase aortic aneurysms and dissections
- CHADSVASc should be repeated annually. Over 3y, 1/3 develop indications for anticoag
- N3 FAs 1g/d had no CV benefits in primary Px– VITAL and ASCEND (EPA and DHA)
- N3 FA icosapent ethyl reduce CV events after MI (2ry Px) – REDUCE-IT
- HRT retards atherosclerosis when start <6y of menopause but not when > 10y after : ELITE (2016)
- Statins decrease CV mortality in patients with Syst AI Rhe Diseases (SARDs)
- DAPT in minor stroke / TIA – meta anaylsis of CHANCE, POINT, FASTER : DAPT reduces recurrent stroke better. Benefit is seen up to 11d. increase bleeding throughout. So short period of DAPT is probably a good choice (BMJ 2018/12/18)

ACTIVE-W : warfarin > clopid AF stroke
ARISTOTLE : apix > warf in AF/stroke
ASCEND : pirf for IPF
ATLANTIS – rtPA 3h
CADISS : asp – anticoag for 2ry Px after carotid / vertebral dissection stroke
CAPACITY : pirf for IPF
CAPRIE : clopid = aspirin
CAST : aspirin in stroke
CHANCE : DAPT for minor stroke / high risk TIA
CLOSE : PFO closure for stroke Px
CLOSURE : PFO closure for stroke Px
DAWN : 6-24h clinical perfusion mismatch – T'ectomy
DECIMAL : decomp hemicraniectomy for malignant MCA
DEFUSE : 6-16h core perfusion mismatch – T'ectomy
DESTINY : decomp hemicraniectomy for malignant MCA
EAFT : warfarin > aspirin AF stroke
ECASS-3 : rtPA 4.5h
ECST : CEA for stroke
ESCAPE : 6h thrombectomy
ESPS : asp-dipyr = aspirin in stroke
ESPRIT : asp-dipyr = aspirin in stroke
EXTEND IA : 6h thrombectomy
EXTEND IA TNK : TNK > rtPA as observed at thrombectomy
INPULSIS : nintedanib for IPF
INSTAGE : ninte + sildenafil not useful for IPF
IST : aspirin in stroke
MR CLEAN : 6h thrombectomy
NASCET : CEA stroke
NAVIGATE ESUS : warfarin for cryptogenic stroke = aspirin; proven superior in meta analysis of NAVIGATE ESUS, CLOSE and PICSS
NINDS rtPA
PC : PFO closure stoke Px
POINT : DAPT 3m more bleeding after minor stroke / high risk TIA
PRoFESS : clopid = asp-dipyr stroke
PROTECT : LAAO non inf to warfarin AF/stroke
REDUCE : PFO closure stroke Px
RELY : dabi = warf AF/stroke, less ICH
RESPECT : PFO closure for stroke Px
REVASCAT : 6h thrombectomy
ROCKET AF : rivarox = warfarin AF/stroke, less ICH, more GIB
SLS – I CPM for SSCl ILD, II: MMF = CPM, III: MMF+pirf vs MMF under way
SWIFT PRIME : 6h thrombectomy
THRACE : 6h thrombectomy
TOMORROW : nintedanib for IPF
WAKE UP : wake up stroke MRI core perfusion mismatch : rtPA
WASID : warfarin < aspirin stroke

ASCEND ARRIVE ASPREE
DECLARE

ODYSSEY OUTCOME
DAWN POINT DEFUSE 3
ADRENAL

Sri lankan trials

Toxicology

Organophosphate

ChE Check mobile app to determine OP concentration
Comparable to blood assays. Overestimates levels. Correction factor 1.53

Can IMS be predicted after OPP?
sfEMG prolonged jitter within 24h predicted IMS. sfEMG recovery paralleled IMS recovery

new Rx modalities for OPP?
NaHCO3, MgSO4 IV, gacyclidine, FFP/albumin (Iran J Med Sci 2012)

Atropine doubling dose titration regimen vs ad hoc administration (IG 2008)
Observational cohort study
Titration regimen arm had more severe OP toxicity but required less atropine and pralidoxime and developed much less atropine toxicity (delirium, hallucinations)

Predicting mortality after OP?
Glasgow coma scale
International Program on Chemical Safety Poison Severity Score (IPCS PSS)

Prevention of IMS with rocuronium – IG - underway

methHb

bed side test for methHb?
A colour chart
methHb > 15% will make blood appear brown
increased methylene blue use and decreased mortality (temporal control)

PCM

paracetamol poisoning severity assessment (2012 Ind I of Pharm, Prof SSR)
pt hx overestimates severity and leads to overuse of antidote
colorimetry is equally accurate and much faster and cheaper than the standard HPLC method

antidote for PCM – cost effectiveness anaylsis (BMC Clin Parm 2012 Prof SSR)
methionine should be preferred for those presenting withing 10h

methionine Vs NAC RCT underway - anuradhapura

snake bite

RV Vs HNV

Paddy field, other	home garden
Leg	upper limb
Local, neuro, caog, renal	local. Coag (3%), renal (3%), no abd pain
Abd pain+	

Long term sequalae of snake bite
Migraine like syndrome
Non specific somatic complains

Local polyspecific antivenom 2016 Toxicon (IG et al)
Whole IgG
Pre clinical neutralization study
RV, cobra, HNV, SSV
Superior to VINS (currently used indian polyspecific AV) except against cobra

Digitalis

New antidote for Nerium oleander cardiotoxicity (Dr IG, Pera)
Fructose 1,6 diphosphate
Underway

Paraquat

Peripheral burning sensation after paraquat predicts high serum levels and poor outcome

New antidote for paraquat?
INTEON (high concentration emetic, purgative and ability to form a gel in stomach reducing absorption)
Superior to Fuller searth
Other Rx tried
Aspirin

Paraquat poisoning – high immunosuppression is not effective – RCT
299 pts
CPM + MPP DXM

Infections

Local dengue vaccine
Vit E – Dr pujitha
Carica papaya – prof SL
Vit C –
Rupatadine
Tranexamic acid – Dr AW

Lepto
NAC – prof SR
PLEX for PAH – prof SL

DM, HTN, ASCVD

TRIUMPH

SGLT2 – empagliflozin had a SL cohort

Linagliptin Vs metformin

ODYSSEY