Diabète de type 2
Prévention cardiovasculaire

JUIN 2016

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Vzw Farmaka asbl – Centre indépendant d'information sur les médicaments

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Visites académiques pour les médecins généralistes

Formulaire de soins aux personnes âgées + Le Formul ℞ info

Etudes de littérature médicale pour :
- **Réunions de consensus INAMI**
- **Fiches de transparence CBIP**
- **…**

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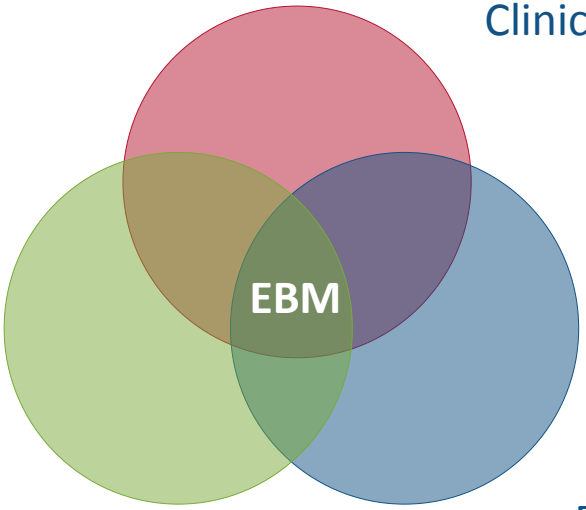
EBM

Evidence Based Medicine



Evidence-based medicine (EBM) requires the integration of the best research evidence with our clinical expertise and our patient's unique values and circumstances

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Méthodologie

- Sources
  - Guides de Pratique Clinique (GPC)
    - Domus Medica: Diabetes mellitus type 2 (2015)
    - ADA : Standard of medical care in diabetes (2015)
    - NICE : Type 2 diabetes in adults : management (2015)
    - NICE : Cardiovascular disease : risk assessment and reduction, including lipid modification (2014)

    Les références de ces publications ont été recherchées
  - Fiche de transparence Diabète de type 2 (sept 2015) + screening (Farmaka) jusque février 2016
  - Réunion de consensus : L'usage rationnel des hypolipidémiants (2014)
- Contenu
  - Prévention cardiovasculaire chez les diabétiques de type 2 via les modifications du style de vie, le contrôle tensionnel, le traitement par statine et l'acide acétylsalicylique
  - À l'exception de la prise en charge hypoglycémiante. À ce propos, se référer à la présentation sur le Diabète de type 2 de juin 2015

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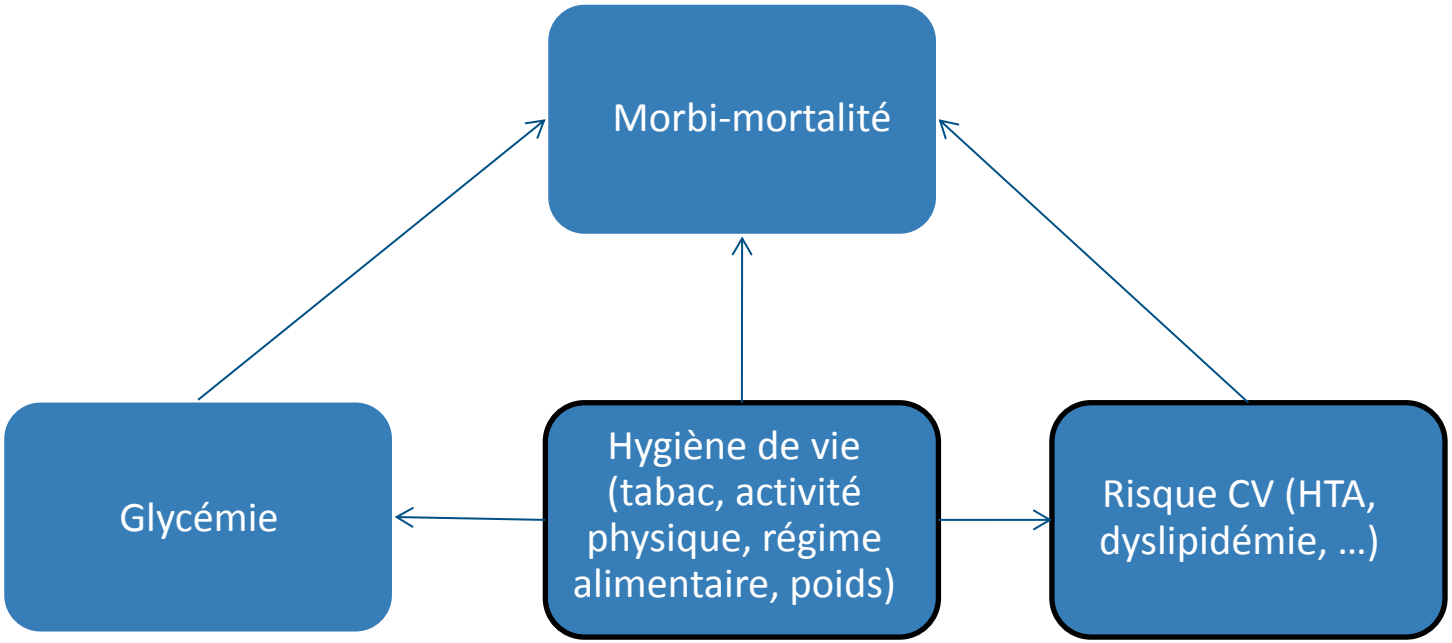
Traiter un patient diabétique

Plus qu'un contrôle glycémique



Plus de preuves d'un bénéfice CV via le contrôle des FR CV que via le contrôle glycémique

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Domus Medica 2015, NICE 2015, ADA 2015, HAS 2013, NHG 2013, CC INAMI 2012, ADA/EASD 2012

Evaluation du risque cardiovasculaire

Evaluer régulièrement le risque CV du patient

Facteurs de risque CV

- Tension artérielle
- Profil lipidique
- Statut tabagique
- Albuminurie
- BMI et périmètre abdominal
- Histoire personnelle et familiale d'événements CV

FR CV (GPC)

→ Prise en charge sur mesure, en fonction du risque CV individuel

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Domus Medica 2015, ADA 2015, NICE 2015

Hygiène de vie

Proposer une hygiène de vie saine à tout patient diabétique

- **Tabac** : données épidémiologiques
  - Sevrage
    - ↘ Mortalité totale
    - ↘ Mortalité par coronaropathie
    - ↘ AVC
  - Réduire de > 50% : pas d'avantage sur la mortalité

- **Alimentation**
  - ↘ Evénements CV majeurs : HR 0.71 (95%CI 0.53-0.96) NNT 125/5ans
    (RCT, haut risque CV, sous-groupe diabétique, régime méditerranéen)

- **Activité physique**
  - ↘ Mortalité totale : HR 0.62 (95% CI 0.49 – 0.78)
    (étude épidémiologique, population diabétique)

TABAC

ALIMENTATION

ACTIVITE PHYSIQUE

MULTI FACTORIEL

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Domus Medica 2015, Doll 2004, KCE 2004, Tverdal 2006, Estruch 2013, Sluik 2012

Contrôle tensionnel : cibles

Viser une TA < 140/90 mmHg

- TA < 140/90 mmHg
  - ↘ Complications CV (coronaropathie, AVC)
  - ↘ Mortalité en lien avec le diabète
  - ↘ Néphropathie

- Valeurs plus strictes ?
  - ↘ Mortalité : pas univoque
  - ↘ AVC
  - ↗ Effets indésirables sérieux

MA PLUS STRICT ? Arguedas

MA PLUS STRICT ? Bangalore

- Guides de pratique

ADA et Domus Medica	TA < 140/90 mmHg (éventuellement si risque AVC élevé : TAS < 130)
NICE	TA < 140/80 mmHg ou si complications du diabète < 130/80

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Domus Medica 2015, ADA 2015, UKPDS-38, Arguedas 2013, McBrien 2012, Bangalore 2011, NICE 2015

Contrôle tensionnel : traitement

En cas de protéinurie : IECA

Sans protéinurie, le choix n'est pas univoque

	Avec protéinurie	Sans protéinurie
Guides de pratique		
	• Débuter IECA (sartan)	• Envisager IECA
Études versus placebo		
IECA	• **↘ Mortalité totale (doses élevées)** • **↘ IR terminale (ESRD)**	• **↘ Mortalité totale**
Sartans	• NS (mortalité totale) • **↘ IR terminale (ESRD)**	• NS (mortalité totale)
Diurétiques, β-bloquants, antagonistes calciques	• Peu de données et/ou dans des populations spécifiques • Le plus souvent, bénéfice démontré (critères CV)	
Comparaisons directes entre antihypertenseurs		
	• Pas univoque • Le plus souvent, pas de différence sur des critères d'évaluation CV	

MA ANTIHTA VS PLACEBO SANS PROTEINURIE Lv2012

MA IECA/SARTAN VS PLACEBO AVEC PROTEINURIE Strippoli 2006

AUTRES VS PLACEBO

DEBUTER IECA

MA ANTIHTA ENTRE EUX Bangalore 2016

MA IECA/SARTAN VS PLACEBO OU AUTRE R/HTA Cheng 2014

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Domus Medica 2015, ADA 2015, NICE 2015, Lv 2012, Cheng 2014, Strippoli 2006, Bangalore 2016, Vijan 2012, Kostis 2005, Haas 2003, Shekelle 2003

Statines : indication

Statine chez la plupart, quel que soit le profil lipidique

- Effet démontré chez les patients diabétiques
  - Avec antécédent CV
  - Sans antécédent CV mais minimum 1 FR CV*

  ! Indépendamment du profil lipidique

- À discuter avec le patient
  - Pas d'autre FR CV : pas de données chez des patients diabétiques
    - Pertinence clinique? Bénéfice absolu dépendant du risque de base
  - Patients jeunes (< 40 ans) ou âgés (> 80 ans): peu de données

* Tabac, HTA, hyperlipidémie, antécédent CV familial, albuminurie, surpoids, obésité

STATINE PREVENTION PRIMAIRE

STATINE PREVENTION SECONDAIRE

INFLUENCE DU RISQUE INITIAL

MORTALITE GROUPE MIXTE

SECURITE STATINES

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Domus Medica 2015, ADA 2015, Costa 2006, Kearney 2008

Statines : comment traiter ?

Fire and forget ?

	Fire and Forget	Treat to Target
GPC	• ADA 2015 • NICE 2015	• Domus Medica 2015 : Cibles – LDL < 100 mg/dl – LDL < 70 mg/dl si ATCD CV
Études	• Majorité des études à dose fixe • 1 RCT : bénéfice CV indépendant de la réponse LDL et du taux de LDL initial	• Comparaison de cibles non étudiée • MA CTT : Extrapolation
	• Pas de données comparant directement les 2 stratégies	

- Quelle statine ?
  - Pravastatine, simvastatine et atorvastatine : les plus étudiées chez les diabétiques
- Quelle puissance/dose ?
  - Sans antécédent CV
    - Pas de données chez les diabétiques
    - NS (puissant vs moins puissant) chez des non diabétiques, à faible risque CV
  - Avec antécédent CV : ↘ SS événements vasculaires majeurs (atorvastatine 80 vs 10 mg)

TREAT TO TARGET VS FIRE AND FORGET

QUELLE STATINE/ QUELLE DOSE ? GPC

PUISSANTES VS MOINS PUISSANTES

DOSES ELEVEES VS FAIBLES

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ADA 2015, NICE 2015, Domus Medica 2015, Tonelli 2011, Sheperd 2006, Collins 2003

Acide acétylsalicylique

Commencer l'acide acétylsalicylique en cas d'antécédents CV

- Sans antécédent CV : pas d'effet démontré chez des patients diabétiques
  - 1 MA dans une population diabétique
    - NS événements CV majeurs
    - NS mortalité CV
    - NS mortalité

SANS ATCD

- Avec antécédent CV : balance bénéfice-risque favorable
  - Pas de données spécifiques chez les patients diabétiques
  - 1 MA dans une population générale (dont 10% sont diabétiques)
    - ↘ SS événements vasculaires majeurs (NNT = 67 par an)
    - NS sur la mortalité CV
    - ↗ SS risque de saignements majeurs (NNH = 526 par an)

AVEC ATCD

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De Berardis 2009, Baigent 2009

Résumé

Traiter un patient diabétique : plus qu'un contrôle glycémique

↓

Evaluer régulièrement le risque CV du patient

↓

Prendre en charge ce risque CV

↓

Hygiène de vie	Contrôle tensionnel	Statine	Acide acétylsalicylique
- Conseils alimentaires - Activité physique - Sevrage tabagique	- TA <140/90 mmHg - IECA si protéinurie	- Chez la plupart des diabétiques - Quel que soit le profil lipidique - Fire and forget?	- Uniquement si ATCD CV

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Annexes

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Annexes – Table des matières

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Cas clinique

Marie-Jeanne, 68 ans, Diabète de type 2 depuis 10 ans

- Antécédents
  - Pas de complications micro- ou macro-vasculaires
  - Hypertension
  - Fumeuse
- Traitement médicamenteux
  - Glucophage 3x850mg
  - Gliclazide retard 60mg
  - Januvia 1x100mg
  - Co-Bisoprolol 1x 10/25mg
  - Cardioaspirine 1x100mg
- Examen clinique
  - TA 135/85 mmHg
  - BMI 26

- Biologie clinique
  - HbA1c 7,1%
  - LDL 92mg/dl cholesterol total 190mg/dl
  - Pas de protéinurie, fonction rénale normale
- Anamnese
  - Pas de plaintes
  - Fume 15 cigarettes/jour
  - Suit les conseils diététiques correctement
  - Marche 2x/semaine environ 30 minutes

Comment adapteriez-vous son traitement ?

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Cas clinique

Marie-Jeanne, 68 ans, Diabète de type 2 depuis 10 ans

- Antécédents — Aucun ?
  - Pas de complications micro- ou macro-vasculaires
  - Hypertension
  - Fumeuse — Sevrage tabac ?
- Traitement médicamenteux
  - Glucophage 3x850mg
  - Gliclazide retard 60mg
  - Januvia 1x100mg
  - Co-Bisoprolol 1x 10/25mg — Remplacer Co-bisoprolol par un IECA ou un Sartan ?
  - Cardioaspirine 1x100mg — Stopper la cardioaspirine ?
- Examen clinique
  - TA 135/85 mmHg — Commencer un sartan ?
  - BMI 26 — Commencer un IECA ?
- Biologie clinique — Commencer une statine ?
  - HbA1c 7,1%
  - LDL 92mg/dl cholesterol total 190mg/dl
  - Pas de protéinurie normale — Pas de statine parce que le LDL est <100mg/dl ?
- Anamnese
  - Pas de plaintes
  - Fume 15 cigarettes/jour
  - Suit les conseils diététiques correctement
  - rche 2x/semaine environ 30 minutes

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Cas clinique - Solution

Marie-Jeanne, 68 ans, Diabète de type 2 depuis 10 ans

Adaptations proposées :

- Sevrage tabagique !
- Débuter une statine indépendamment de sont taux de LDL étant donné son diabète + HTA
- Stopper la cardioaspirine : pas d'indication en l'absence d'antécédents cardiovasculaires, en raison de la balance bénéfice/risque défavorable

Adaptations non nécessaires :

- Pas d'indication obligatoire pour un inhibiteur du système RAA étant donné l'absence de protéinurie
- La tension artérielle est actuellement < 140/90mmHg ce qui est acceptable

Facteurs de risque CV selon les guides de pratique

	Domus Medica	ADA*	NICE**
TA	À chaque consultation	À chaque consultation	1x/an, QRISK
Profil lipidique	1x/an	Au moment du diagnostic et tous les 1 à 2 ans par la suite (aussi dans le but de vérifier la compliance thérapeutique)	Au moment du diagnostic , QRISK
Statut tabagique	1x/an	À chaque consultation	QRISK
Albuminurie	1x/an	1x/an	Si insuffisance rénale stade 4 ou 5
BMI et périmètre abdominal	1x/an	Au moment du diagnostic (aussi utilisé pour décider si on commence une statine)	QRISK
Antécédents CV personnels	1x/an	Au moment du diagnostic (aussi utilisé pour décider si on commence une statine)	**
Antécédents CV familiaux	1x/an	Pas mentionné	QRISK
		*ADA mentionne ce qui doit être évalué chez un patient diabétique, on ne mentionne pas de façon spécifique quels facteurs doivent être évalués dans le cadre du risque CV	** NICE utilise pour l'évaluation du risque CV un calculateur QRISK; on mentionne que ce QRISK est adapté aux personnes qui n'ont pas encore eu de maladie CV

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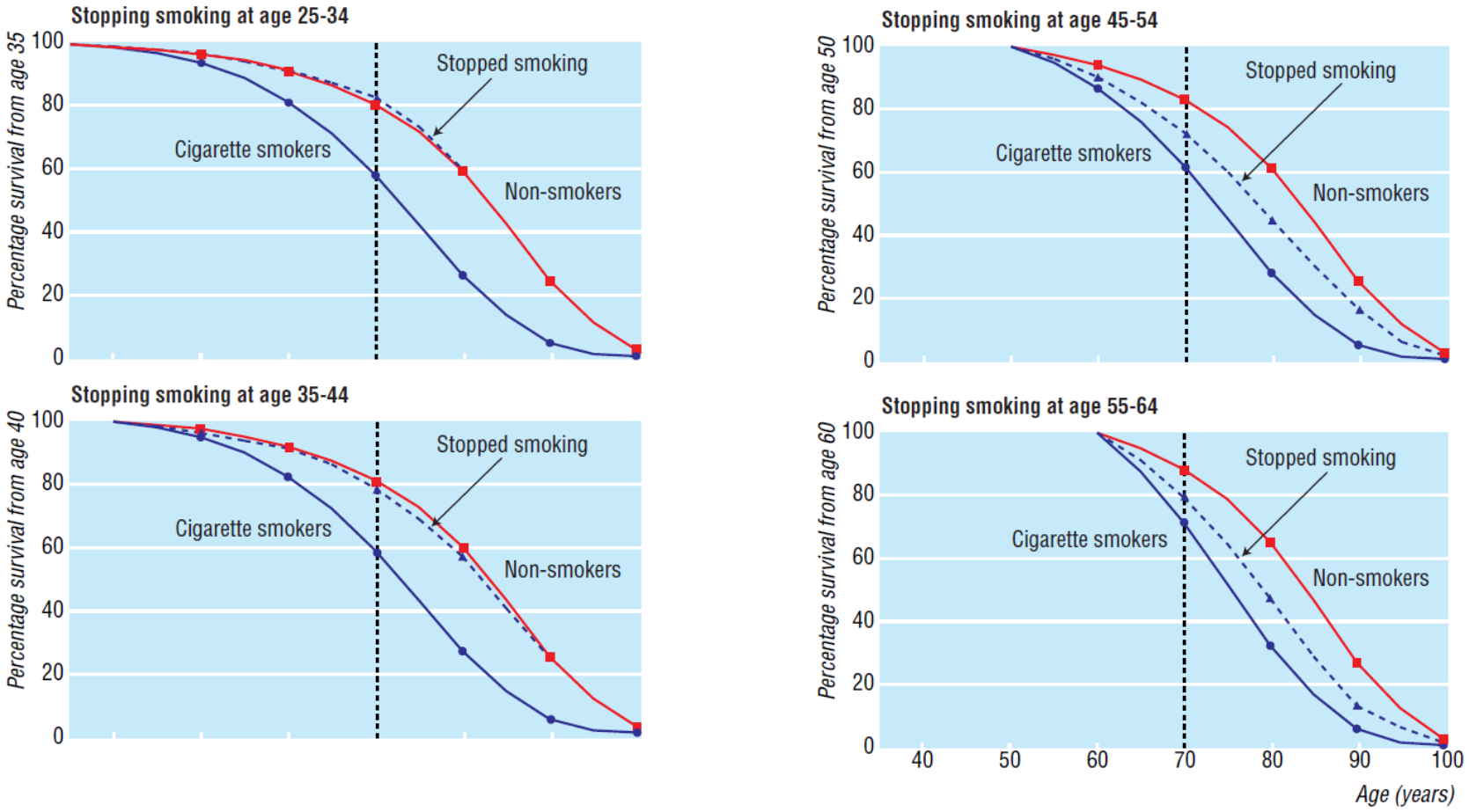
Domus Medica 2015, ADA 2015, NICE 2015

Sevrage tabagique



Doll 2004

Régime méditerranéen

Estruch 2013						
Design	Population	n	Duration	Intervention	Outcome	Result
RCT	*High CV risk** *No CV disease* *55 to 88 y* *49% diabetes*	7447	Median follow-up 4.8 y	Mediterranean diet + extra-virgin olive oil vs Mediterranean diet + mixed nuts vs Control diet**	Major CV events *** (I)	**MD + olive oil 3.8% vs 4.4%** **HR = 0.70 (95% CI 0.54 to 0.92)******
						MD + nuts 3.4% vs 4.4% **HR = 0.72 (95% CI 0.54 to 0.96)******
					Stroke (II)	**MD + olive oil HR = 0.67 (95% CI 0.46 to 0.98)**
						MD + nuts HR = 0.54 (95% CI 0.35 to 0.84)
					Myocardial infarction (II)	MD + olive oil HR = 0.80 (95% CI 0.21 to 1.26)
						MD + nuts HR = 0.74 (95% CI 0.46 to 1.19)
					Death from CV causes (II)	MD + olive oil HR = 0.69 (95% CI 0.41 to 1.16)
						MD + nuts HR = 1.01 (95% CI 0.61 to 1.66)
					Death from any cause (II)	MD + olive oil HR = 0.82 (95% CI 0.64 to 1.07)
						MD + nuts HR = 0.97 (95% CI 0.74 to 1.26)
	Prespecified subgroupanalysis in patients with diabetes	3614		Combined mediterranean diets vs Control diet	Major CV events *** (I)	**5.0% vs 5.8%** **HR = 0.71 (95% CI 0.53 to 0.96)** **NNT = 125/4.8y**

* Participants had either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated LDL, low HDL, overweight or obesity, or a family history of preamature coronary heart disease

**Control diet = advise to reduce dietary fat. During the first 3 years of the trial, they received only a leaflet on yearly basis. The protocol was changed in 2006, were they received personal advice and were invited to group sessions with the same frequency and intensity as those in the mediterranean diet groups.

*** The primary end point was a composite of myocardial infarction, stroke, an death from cardiovascular causes

**** Multivariable adjusted

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Régime méditerranéen

Apports élevés	• Fruits, légumes, légumineuses et noix • Hydrates de carbone complexes (grains entiers)
Apports modérés	• Poisson • Volaille • Produits laitiers (principalement fromage et yaourt)

Source principale de graisses : Huiles végétales (en particulier huile d'olive)

Apports limités	• Viande rouge et charcuteries
Apports très limités	• Sucreries telles que pâtisseries, soda, bonbons, …

Apport modéré de vin rouge (pendant le repas)

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Mente 2009, Estruch 2013, SSMG 2008, Sofi 2010

Activité physique – Étude de cohorte

Sluik 2012						
Design	Population	n	Duration	Intervention	Outcome	Result
Prospective cohort study	*Diabetes (no information to distinguish between type 1 and type 2)*	5859	Median follow-up 9.4 y	Total physical activity* Moderately active vs Inactive**	CV mortality (I)	**HR*** 0.51 (95% CI 0.32 to 0.81)**
					Total mortality (I)	**HR*** 0.62 (95% CI 0.49 to 0.78)**
				Total physical activity* Active vs Inactive**	CV mortality (I)	HR*** 0.62 (95% CI 0.38 to 1.01)
					Total mortality (I)	**HR*** 0.74 (95% CI 0.59 to 0.94)**

*Total physical activity was investigated using the Cambridge Physical Activity Index, which combines self-reported occupational acitivity with time participating in cycling and sports.
** Participants were divided in 4 categories, that is, inactive (sedentary job and no recreational activity), moderately inactive, moderately active, and active (sedentary job with > 1hour recreational activity per day, standing of physical job with some recreational activity, or an heavy manual job)
*** HRs were adjusted for sex, disease duration, use of diabetes related medication; self reported myocardial infarction, stroke, or cancer; alcohol consumption; smoking status, smoking duration and number of cigarettes currently smoked; education; energy intake; and factor scores for the first 3 patterns derived form factor analysis on 16 food groups. A sensitivity analyses with additional adjustment for HbA1c level, BMI, and systolic blood pressure did not affect the risk estimates. Excluding participants with comorbidities at baseline (prevalent cases of MI, stroke and cancer; and participants with follow up of less than 2 years), led to lower HRs.

Hygiène de vie - Prise en charge multifactorielle

Wing 2013 (Look AHEAD)						
Design	Population	n	Duration	Intervention	Outcome	Result
RCT	*Type 2 diabetes aged 45–74 y BMI ≥25 (≥27 if taking insulin) Run in 2w****	5145	9.6 y results*****	Intensive Lifestyle Intervention (ILI) * vs Diabetes Support and Education (DSE)**	Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina (I)	1.83 vs 1.92 events per 100 person-years HR = 0.95 (95%CI 0.83 to 1.09) P = 0.51
					Weight loss (I)	**–6% vs – 3.5% (P < .001)**

* Involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity (The ILI included a "toolbox" to help participants achieve and maintain the study's weight loss and activity goals. Use of the "toolbox" was based on a pre-set algorithm and assessment of participant progress. After the first 6 months, the "toolbox" algorithm included use of a weight loss medicine (orlistat) and/or advanced behavioral strategies for individuals who had difficulty in meeting the trial's weight or activity goals. Specific protocols were used to determine when to initiate medication or other approaches, to monitor participants, and to determine when to stop a particular intervention.

** Participants assigned to DSE attended the initial pre-randomization diabetes education session (described below) and were invited to 3 additional group sessions during the first year. A standard protocol was used for conducting these sessions, which provided information and opportunities for discussing topics related to diet, physical activity, and social support. However, the DSE group was not weighed at these sessions and received no counseling in behavioral strategies for changing diet and activity.

*** Prior to randomization, all study participants were required to complete a 2-week run-in period which included successful self-monitoring of diet and physical activity, and they were provided an initial session of diabetes education with particular emphasis on aspects of diabetes care related to the trial such as management of hypoglycemia and foot care. The session stressed the importance of eating a healthy diet and being physically active for both weight loss and improvement of glycemic control. All individuals who smoked were encouraged to quit and were provided self-help materials and/or referral to local programs as appropriate.

**** The trial, initially planned for 13.5 years, was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years.

Biais potentiel : moindre usage de médications à effet CV (statine, antihypertenseurs) dans le groupe intervention, mais il ne s'agissait pas d'un critère d'évaluation dans cette étude

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Cibles tensionnelles plus strictes

Arguedas 2013 – Systolic blood pressure targets						
Design	Population	N/n	Duration	Intervention	Outcome	Result
MA	*Adults* *DM II* *With elevated blood pressure**	1/4734 (ACCORD)	4.7 y	SBD < 130 vs SBD <140-160** (targets)	Total mortality (I)	RR = 1,05 (95% CI 0.84 to 1.30)
					Stroke (I)	**1.5 % vs 2.6%** **RR = 0,58 (95% CI 0.39 to 0.88)** **NNT = 91**
					Myocardial infarction (I)	RR = 0.88 (95% CI 0.71 to 1.11)
					Congestive hearth failure (I)	RR = 0.93 (95% CI 0.69 to 1.24)
					ESRF (I)	RR = 1.02 (95% CI 0.71 to 1.46)
					Total serious adverse events (I)***	RR = 1.01 (95% CI 0.91 to 1.13)
					Other serious adverse events (I) attributed to blood pressure medications ****	**3.3% vs 1.3%** **RR = 2.58 (95%CI 1.70 to 3.91)** **NNH = 50**

Only 1 RCT was included in this meta-analysis: ACCORD study. Low quality of evidence, only 1 RCT, unblinded
* In ACCORD study patients had high CV risk to be included.
** The intervention in the ACCORD study was SBD <120 vs <140 (targets). Achieved systolic blood pressure was 119.3 mmHg in the intensive-therapy group and 133.5 mmHg in the standard-therapy group.
*** total serious adverse events was not reported in ACCORD BD trial. In Cochrane review, they calculated the sum of total mortality, non-fatal MI, non fatal stroke, non fatal heart failure, end stage renal disease or need for dialysis and other serious adverse events attributed to blood pressure medications.
**** The ACCORD BD 2010 investigators reported separately other serious adverse events attributed to blood pressure medications, including hypotension, syncope, bradycardia or arrhythmia, hyperkalaemia, angioedema, and renal failure. Serious adverse events are events that are life-threatening, cause permanent disability, or necessitate hospitalization.

Cibles tensionnelles plus strictes

Arguedas 2013 – Diastolic blood pressure targets						
Design	Population	N/n	Duration	Intervention	Outcome	Result
MA	*Adults* *DM II* *With elevated blood pressure*	4/2580 (ABCD-H, ABCD-N, ABCD-2V and HOT)	1.9 to 5 y	DBD < 85 vs DBD < 90-100* (targets)	Total mortality (I)	RR = 0.73 (95% CI 0.53 to 1.01)
					Stroke (I)	RR = 0.67 (95% CI 0.42 to 1.05)
					Myocardial infarction (I)	RR = 0.95 (95% CI 0.64 to 1.40)
					Congestive hearth failure (I)	RR = 1.06 (95% CI 0.58 to 1.92)
					ESRF (I)	Not reported
					Total serious adverse events (I)	Not reported
					Other serious adverse events (I)	Not reported

* Achieved blood pressure was 128/76 mmHg versus 135/83 mmHg.

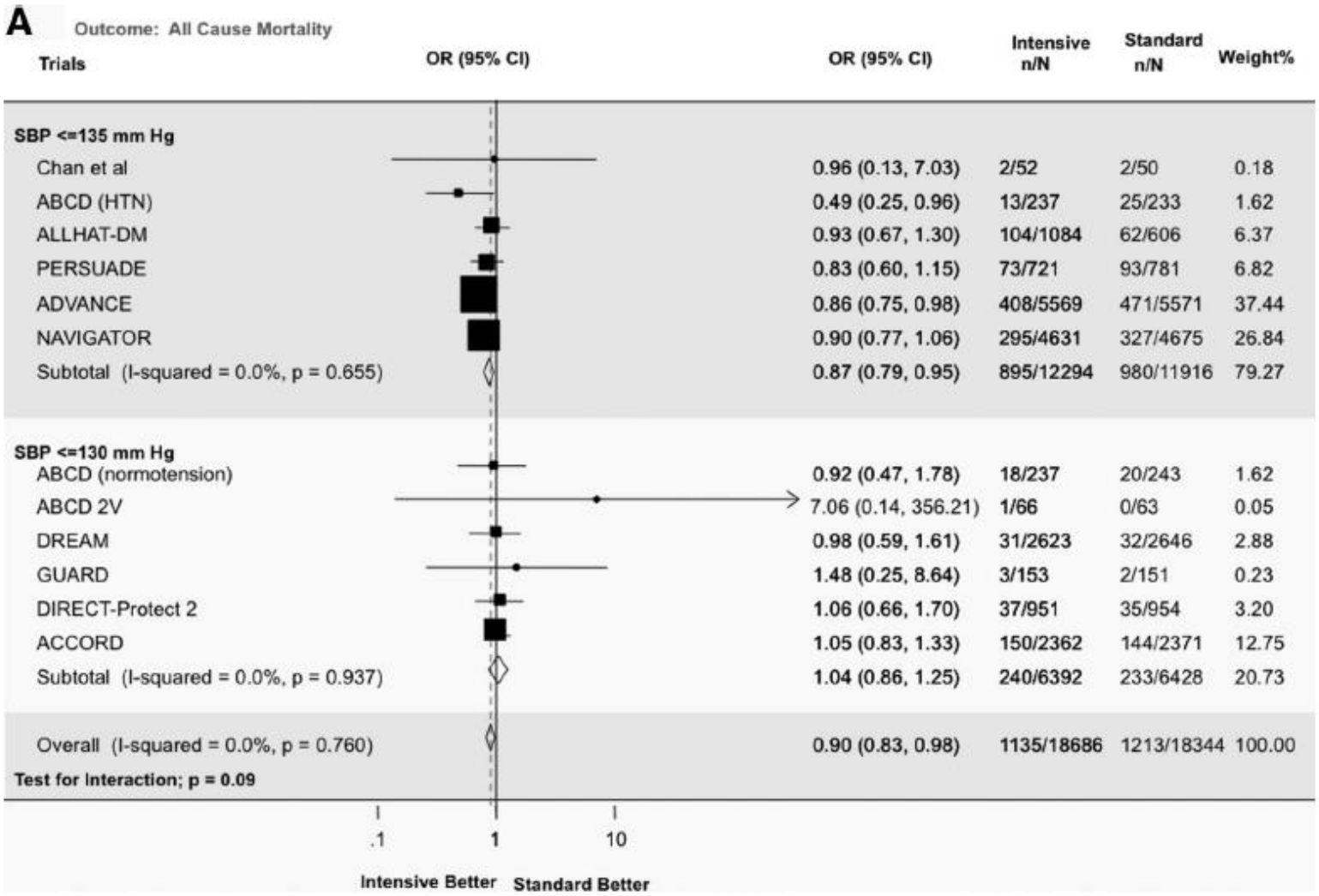
- Very low quality of evidence due to high risk of bias (inadequate sequence generation, no blinding, subgroup analysis and early determination).

Cibles tensionnelles plus strictes

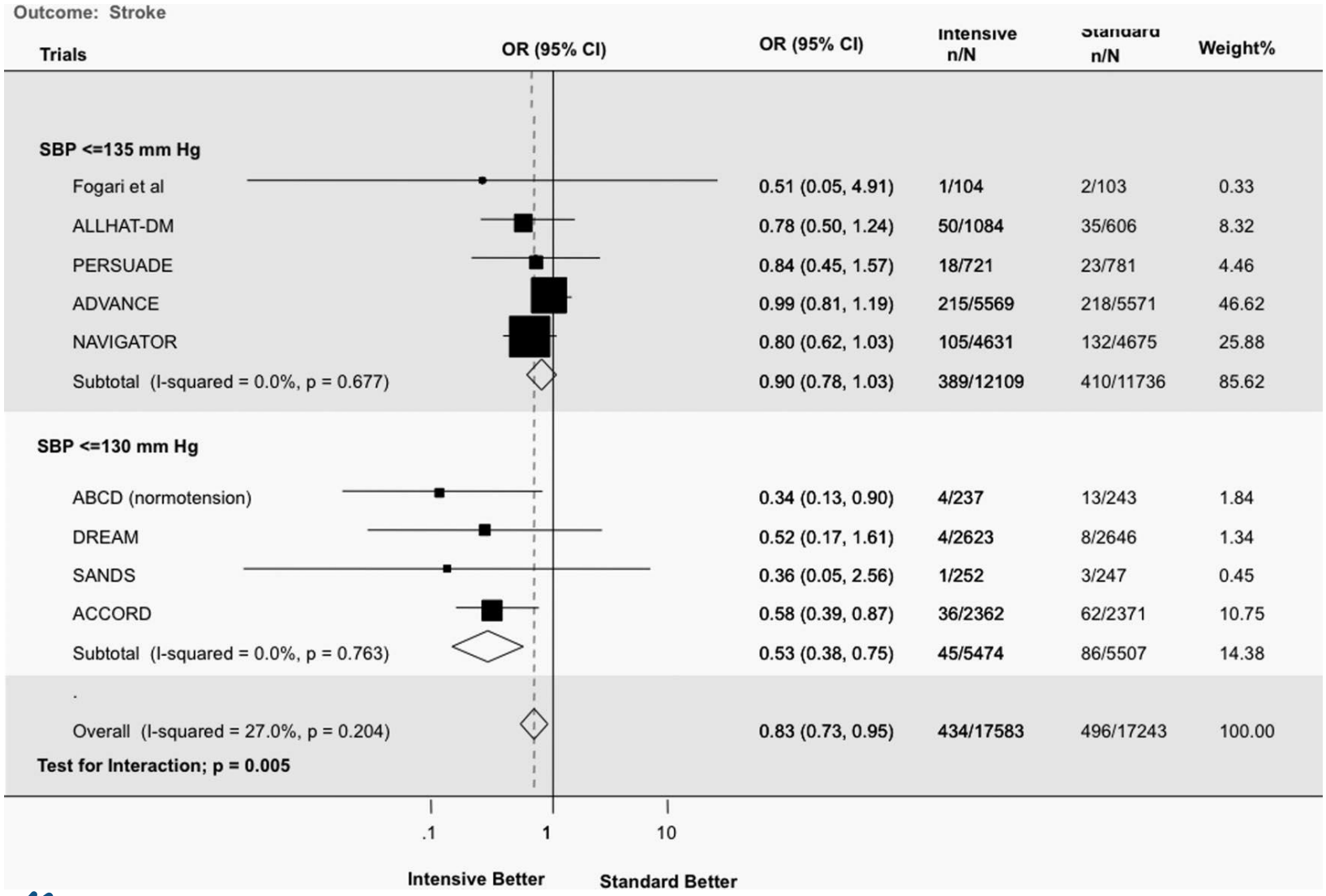
Bangalore 2011						
Design	Population	N/n	Duration	Intervention	Outcome	Result
MA	*Adults DM II or impaired fasting glucose/ impaired glucose tolerance*	13/ 37736	1.9 to 6.5 y	SBD ≤ 135 vs SBD ≤ 140* (achieved)	**Total mortality (I)**	**OR = 0.90 (95% CI 0.83 to 0.98)**
					CV mortality (I)	OR = 0.93 (95% CI 0.82 to 1.06)
					Stroke (I)	**OR = 0.83 (95% CI 0.73 to 0.95)**
					Myocardial infarction (I)	OR = 0.92 (95% CI 0.80 to 1.06)
					Hearth failure (I)	OR = 0.90 (95% CI 0.75 to 1.06)
					ESRF (I)	No difference, data not shown
					Total serious adverse events (I)**	**OR = 1.20 (95% CI 1.08 to 1.32)** SBD ≤ 130 vs SBD ≤ 140 **OR = 1.40 (95% CI 1.19 to 1.64)**

* These terms are based on mean achieved systolic BP and are not necessarily the strategy used in the trial (not all trials tested a BP strategy). Of the 13 trials, only 5 tested a BP strategy (intensive versus standard) by design.
** The serious adverse effects were variously defined as events that are life-threatening, cause permanent disability, or necessitate hospitalization or withdrawal owing to adverse effects.

Cibles tensionnelles plus strictes - Bangalore 2011



Cibles tensionnelles plus strictes - Bangalore 2011



Antihypertenseurs vs placebo chez diabétiques (+/- HTA) sans protéinurie

Lv 2012

Design	Population	Duration	N/n	Intervention	N/n	Outcome		Result
SR + MA of RCT's	*Diabetes mellitus (type 1 and type 2***)* *Normoalbuminuria (albumin excretion rate < 30mg/d)* *Age ≥ 18y* *With or without hypertension*	6 to 72m	26/61264	ACE-i vs Placebo/no treatment	6/11350	All cause mortality (I)*		**RR = 0.84 (95% CI 0.73 to 0.97)**
					3/10504	ESRD (I) ****		RR = 1.94 (95% CI 0.6 to 5.70)
					6/11791	Adverse events (I)	Cough	**RR = 1.84 (95% CI 1.24 to 2.72)**
							Headache	NS
							Hyperkalemia	NS
				Sartan vs Placebo/no treatment	5/7653	All cause mortality (I)*		RR = 1.12 (95% CI 0.88 to 1.41)
					3/6217	ESRD (I)****		RR = 0.50 (95% CI 0.09 to 2.71)
					3/1592	Adverse events (I)	Cough	NS
							Headache	NS
							Hyperkalemia	NS
				ACE-I vs Sartan	2/4303	All cause mortality (I)		RR = 1.02 (95% CI 0.85 to 1.22)
				ACE-I vs CCB	5/1284	All cause mortality (I)		RR = 0.84 (95% CI 0.26 to 2.73)

* The only hard endpoint measured in this meta-analysis is mortality; other endpoints are for example blood pressure or albuminuria.
** Authors searched for different antihypertensive agents such as ACEi, ARB, calcium channel blockers , betablockers and diuretics; versus placebo, but only studies on ACE-I versus placebo and ARB versus placebo were found. The comparison of CCB versus placebo only studied new onset microalbuminuria
*** Most studies enrolled only type 2 diabetic patients
**** Note that very few patients in these studies progressed to the end point of doubling of serum creatinine or ESRD

Antihypertenseurs vs placebo chez diabétiques
(+/- HTA) sans protéinurie – IECA vs placebo – Lv2012

Analysis 1.2. Comparison 1 ACEi versus placebo/no treatment, Outcome 2 All-cause mortality.

Review: Antihypertensive agents for preventing diabetic kidney disease

Comparison: 1 ACEi versus placebo/no treatment

Outcome: 2 All-cause mortality

Study or subgroup	ACEi n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ADVANCE Study 2009	229/3931	267/3946		66.6 %	0.86 [0.73, 1.02]
BENEDICT Study 2004	2/301	1/300		0.3 %	1.99 [0.18, 21.87]
HOPE Study 2000	106/1256	126/1182		32.2 %	0.79 [0.62, 1.01]
Kvetny 2001	0/43	0/46			Not estimable
RASS Study 2002	1/94	1/95		0.3 %	1.01 [0.06, 15.92]
Ravid 1998	3/77	2/79		0.6 %	1.54 [0.26, 8.96]
Total (95% CI)	**5702**	**5648**		**100.0 %**	**0.84 [0.73, 0.97]**

Total events: 341 (ACEi), 397 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.27$, $df = 4$ ($P = 0.87$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.39$ ($P = 0.017$)

Test for subgroup differences: Not applicable

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Antihypertenseurs vs placebo chez diabétiques (+/- HTA) sans protéinurie – Sartans vs placebo – Lv2012

Analysis 2.2. Comparison 2 ARB versus placebo/no treatment, Outcome 2 All-cause mortality.

Review: Antihypertensive agents for preventing diabetic kidney disease

Comparison: 2 ARB versus placebo/no treatment

Outcome: 2 All-cause mortality

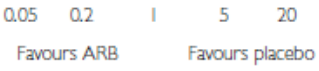
Study or subgroup	ARB n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
DIRECT Studies 2009	7/711	5/710		4.2 %	1.40 [0.45, 4.38]
Perrin 2008	0/7	0/6			Not estimable
RASS Study 2002	1/96	1/95		0.7 %	0.99 [0.06, 15.59]
ROADMAP Study 2009	32/2233	19/2216		17.2 %	1.67 [0.95, 2.94]
TRANSCEND Study 2009	96/785	96/794		77.9 %	1.01 [0.78, 1.32]
Total (95% CI)	**3832**	**3821**		**100.0 %**	**1.12 [0.88, 1.41]**

Total events: 136 (ARB), 121 (Placebo/no treatment)

Heterogeneity: Tau² = 0.0; Chi² = 2.66, df = 3 (P = 0.45); I² =0.0%

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable



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IECA versus placebo chez diabétiques
(30% avec microalbuminurie)

HOPE 2000						
Design	Population	n	Duration	Intervention	Outcome	Result
RCT	*≥55 y* *Diabetes* *Previous CVD or ≥1 other CVRF*** *50% HTA* *Exclusion criteria :* • *Heart failure* • *Creat>2.3 mg/dl* • *dipstickprot. (>+1)*	3577	4.5y	Ramipril 10 mg/d (n = 1808) vs Placebo (n = 1769)	**combined CV endpoint* (I)**	**RR = 0.75 (95% CI 0.64 to 0.88)**
					Total mortality (II)	**RR = 0.76 (95% CI 0.63 to 0.92)**
					Cardiovascular mortality (I)	**RR = 0.63 (95% CI 0.49 to 0.79)**
					Stroke (I)	**RR = 0.67 (95% CI 0.50 to 0.90)**
					Myocardial infarction (I)	**RR = 0.78 (95% CI 0.64 to 0.94)**
					ESRF	NS
					Total serious adverse events	Not reported, run-in

* This end point is a combined end point of MI, stroke and cardiovascular death
** total cholesterol >5.2 mmol/l, HDL cholesterol ≤ 0.9 mmol/l, hypertension, known microalbuminuria, or current smoking

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IECA versus placebo chez diabétiques
(avec protéinurie)

DIABHYCAR 2004

Design	Population	n	Duration	Intervention	Outcome	Result
RCT	*Diabetes type 2* *Albuminurie ≥ 20mg/l* *50 y* *55% hypertensive* *Exclusion criteria :* • *Creat >1,7 mg/dl* • *Insulin, ACEI or ARB* • *Chronic heart failure* • *Recent AMI* • *Urinary tract infection* • *Previous intolerance to an ACE-I*	4912	Median 47 months	Ramipril 1,25mg/d (n = 2443) vs Placebo (n = 2469)	Gecombineerd CV eindpunt* (I)	RR = 0.97 (95% CI 0.85 to 1.11)
					Total mortality (II)	RR = 1.04 (95% CI 0.90 to 1.20)
					Cardiovascular mortality (I)	RR = 1.07 (95% CI 0.85 to 1.35)
					Non fatal stroke (I)	RR = 1.07 (95% CI 0.80 to 1.44)
					Non fatal myocardial infarction (I)	RR = 0.89 (95% CI 0.61 to 1.29)
					Non fatal heart failure (I)**	RR = 0.84 (95% CI 0.62 to 1.14)
					ESRF (I)	RR = 0.40 (95% CI 0.13 to 1.30)
					Serious adverse events	NS 43.2% vs 44.4%

* this end point is a combined incidence of cardiovascular death (including sudden death), non-fatal acute myocardial infarction, stroke, heart failure requiring admission to hospital, and end stage renal failure (defined as requirement for haemodialysis or kidney transplant)
** requiring hospital admission or the intervention of a mobile coronary care unit

Autres antihypertenseurs vs placebo chez diabétiques

- Études versus placebo
  - B-bloquants: bénéfice SS (population avec décompensation cardiaque) sur la mortalité
  - Diurétiques : bénéfice SS (population plus âgée) sur un critère CV composite et sur la mortalité totale et CV
  - Antagonistes calciques : bénéfice (population plus âgée, post hoc pour le diabète) sur certains critères CV, mais pas la mortalité

IEC/Sartan chez diabétiques
(+/- HTA) avec protéinurie

Strippoli 2006

Design	Population	Duration	Intervention	N/n	Outcome	Result
SR + MA of RCT's	*Diabetes mellitus (type 1 and type 2)* Diabetic kidney disease (albumin excretion > 30mg/d) Age ≥ 18y With or without hypertension*	> 6m	ACE-i vs Placebo/no treatment	21/7295	All cause mortality (I)	RR = 0.91 (95% CI 0.71 to 1.17)** ACE-I at maximum tolerable dose vs placebo: **RR = 0.78 (95% CI 0.61 to 0.98)**
				10/6819	ESRD (I)	**RR = 0.60 (95% CI 0.39 to 0.93)**
				10/7087	Cough (I)	**RR = 3.17 (95% CI 2.29 to 4.38)**
				4/6186	Headache (I)	RR = 0.92 (95% CI 0.33 to 2.53)
				2/1219	Hyperkalemia (I)	RR = 0.85 (95%CI 0.32 to 2.21)
			Sartan vs Placebo/no treatment	5/3409	All cause mortality (I)	RR = 0.99 (95% CI 0.85 to 1.17)***
				3/3251	ESRD (I)	**RR = 0.78 (95% CI 0.67 to 0.91)**
				2/194	Cough	RR = 4.93 (95% CI 1.00 to 24.35)
				1/91	Headache	RR = 0.70 (95% CI 0.03 to 16.68)
				1/1148	Hyperkalemia	**RR = 5.41 (95% CI 1.20 to 24.28)**
			ACE-I vs Sartan	3/307	All cause mortality (I)	RR = 0.92 (95% CI 0.31 to 2.78)
					ESRD	Not reported

* The four studies that compared ARB with placebo all enrolled hypertensive patients with type 2 diabetes. There was no evidence that the effect of ACE-I on mortality and EXRD varied according to type of diabetees

** This analysis was dominated by two studies which contributed 49.68% and 37.78% of the weight to the summary estimate (DIABHYCAR 2004; HOPE 2000)

*** This analysis was dominated by two studies, which contributed 64.6%and 34.9%of the weight to the summary estimate (IDNT 2001; RENAAL 2001)

IECA versus placebo chez diabétiques
(+/- HTA) avec protéinurie – Strippoli 2006

Analysis 1.1. Comparison 1 ACEi versus placebo/no treatment, Outcome 1 All-cause mortality.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: 1 ACEi versus placebo/no treatment

Outcome: 1 All-cause mortality

Study or subgroup	ACEi n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Half or less maximum tolerable dose					
AIPRI 1996	2/6	1/15		1.3 %	5.00 [0.55, 45.39]
Bojestig 2001	0/37	0/18			Not estimable
Capek 1994	0/9	0/6			Not estimable
Chase 1993	0/6	0/9			Not estimable
Cordonnier 1999	0/9	0/10			Not estimable
DIABHYCAR 2004	334/2443	324/2469		49.7 %	1.04 [0.90, 1.20]
Garg 1998	0/7	0/4			Not estimable
Nankervis 1998	0/17	3/14		0.8 %	0.12 [0.01, 2.13]
Ravid 1993	0/49	0/45			Not estimable
Romero 1993	0/13	0/13			Not estimable
Sano 1994	1/31	0/31		0.6 %	3.00 [0.13, 70.92]
Subtotal (95% CI)	**2627**	**2634**		**52.4 %**	**1.18 [0.41, 3.44]**

Total events: 337 (ACEi), 328 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 4.55$, df = 3 (P = 0.21); $I^2 = 34\%$

Test for overall effect: Z = 0.31 (P = 0.76)

DIABHYCAR

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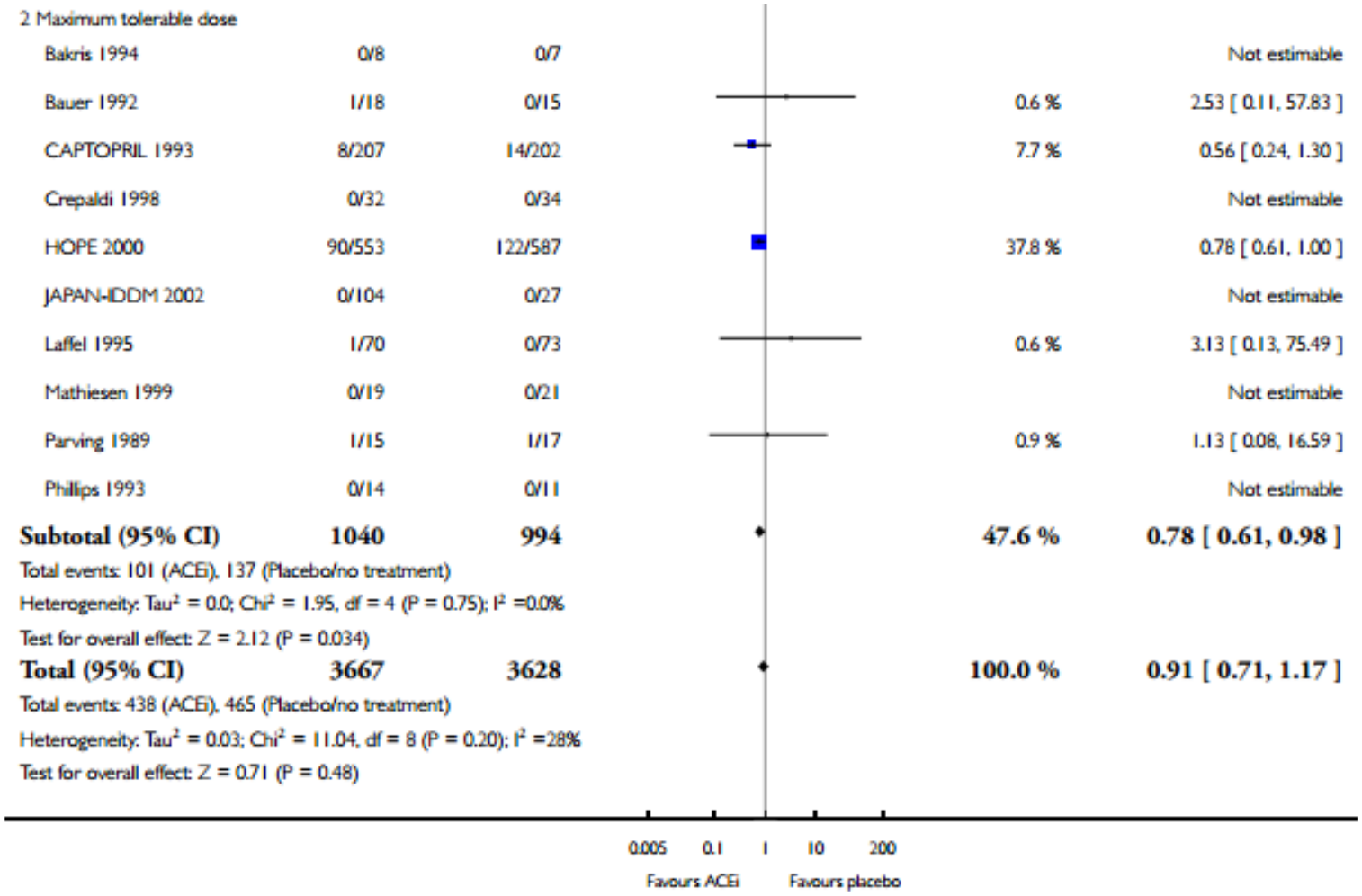
Strippoli 2006

IECA versus placebo chez diabétiques
(+/- HTA) avec protéinurie – Strippoli 2006



HOPE

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Strippoli 2006

IECA versus placebo chez diabétiques
(+/- HTA) avec protéinurie – Strippoli 2006

Analysis 1.4. Comparison 1 ACEi versus placebo/no treatment, Outcome 4 End-stage kidney disease.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: 1 ACEi versus placebo/no treatment

Outcome: 4 End-stage kidney disease

Study or subgroup	ACEi n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Capek 1994	0/9	0/6			Not estimable
CAPTOPRIL 1993	20/207	31/202		69.4 %	0.63 [0.37, 1.07]
DIABHYCAR 2004	4/2443	10/2469		14.4 %	0.40 [0.13, 1.29]
HOPE 2000	5/553	6/587		13.9 %	0.88 [0.27, 2.88]
JAPAN-IDDM 2002	0/104	0/27			Not estimable
Marre 1987	0/10	0/10			Not estimable
Mathiesen 1999	0/19	0/21			Not estimable
Parving 1989	0/15	3/17		2.3 %	0.16 [0.01, 2.88]
Ravid 1993	0/49	0/45			Not estimable
Romero 1993	0/13	0/13			Not estimable
Total (95% CI)	**3422**	**3397**		**100.0 %**	**0.60 [0.39, 0.93]**

Total events: 29 (ACEi), 50 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.71$, $df = 3$ ($P = 0.64$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.28$ ($P = 0.023$)

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Strippoli 2006

Sartans versus placebo chez diabétiques
(+/- HTA) avec protéinurie – Strippoli 2006

Analysis 2.1. Comparison 2 AIIRA versus placebo/no treatment, Outcome 1 All-cause mortality.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: 2 AIIRA versus placebo/no treatment

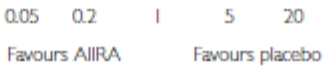
Outcome: 1 All-cause mortality

Study or subgroup	AIIRA n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
IDNT 2001	87/579	93/569		34.9 %	0.92 [0.70, 1.20]
IRMA-2 2001	3/389	1/201		0.5 %	1.55 [0.16, 14.81]
Muirhead 1999	0/54	0/24			Not estimable
RENAAL 2001	158/751	155/762		64.6 %	1.03 [0.85, 1.26]
Tan 2002	0/40	0/40			Not estimable
Total (95% CI)	**1813**	**1596**		**100.0 %**	**0.99 [0.85, 1.17]**

Total events: 248 (AIIRA), 249 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 0.07 (P = 0.95)



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Strippoli 2006

Sartans versus placebo chez diabétiques
(+/- HTA) avec protéinurie – Strippoli 2006

Analysis 2.4. Comparison 2 AIIRA versus placebo/no treatment, Outcome 4 End-stage kidney disease.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: 2 AIIRA versus placebo/no treatment

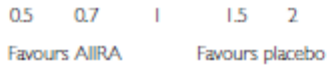
Outcome: 4 End-stage kidney disease

Study or subgroup	AIIRA n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
IDNT 2001	82/579	101/569		33.4 %	0.80 [0.61, 1.04]
Parving 2001a	0/389	0/201			Not estimable
RENAAL 2001	147/751	194/762		66.6 %	0.77 [0.64, 0.93]
Total (95% CI)	**1719**	**1532**		**100.0 %**	**0.78 [0.67, 0.91]**

Total events: 229 (AIIRA), 295 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 3.18 (P = 0.0015)



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Strippoli 2006

IECA/Sartans chez diabétiques
(+/- HTA) avec ou sans protéinurie (vs placebo ou autre R/)

Cheng 2014						
Design	Population	Duration	N/n	Intervention	Outcome	Result
SR + MA of RCT's	*Diabetes mellitus (type 1 and type 2)* *With or without HTA* *With or without proteinuria*	> 12m	23/32827	ACE-i vs Placebo or active drugs**	All cause mortality (I)	**RR = 0.87 (95% CI 0.78 to 0.98)**
					CV mortality (I)	**RR = 0.83 (95% CI 0.70 to 0.99)**
					Major CV events (II)*	**RR = 0.86 (95% CI 0.77 to 0.95)**
					Myocardial infarction (II)	**RR = 0.79 (95% CI 0.65 to 0.95)**
					Stroke (II)	RR = 0.95 (95% CI 0.86 to 1.04)
					Congestive heart failure (II)	**RR = 0.81 (95% CI 0.71 to 0.93)**
			13/23867	ARB vs Placebo or active drugs**	All cause mortality (I)	RR = 0.94 (95% CI 0.82 to 1.08)
					CV mortality (I)	RR = 1.21 (95% CI 0.81 to 1.80)
					Major CV events (II)	RR = 0.94 (95% CI 0.85 to 1.01)
					Myocardial infarction (II)	RR = 0.89 (95% CI 0.74 to 1.07)
					Stroke (II)	RR = 1.00 (95% CI 0.89 to 1.12)
					Congestive heart failure (II)	**RR = 0.70 (95% CI 0.59 to 0.82)**

* Major CV events were defined as the composite of CV death, nonfatal myocardial infarction (MI) an stroke, congestive heart failure, and coronary artery bypass grafting or percutaneous coronary intervention
** The results were similar when ACE-I compared with placebo or active treatment (p = 0,49 for interaction)

Comparaison antihypertenseurs chez diabétiques
majoritairement +HTA et sans protéinurie

Bangalore 2016

Design	Population	Duration	N/n	Intervention	Outcome	Result
SR + MA of RCT's	*Diabetes or impaired fasting glucose Exclusion: cohorts with heart failure* *Majority hypertension Majority without proteinuria*	Studies > 12m Mean follow up 3.8y	19/25414	RAS blockers vs Other antihypertensives **	All cause mortality	RR = 0.99 (95% CI 0.93 to 1.05)
					CV mortality	RR = 1.02 (95% CI 0.83 to 1.24)
					Myocardial infarction	RR = 0.87 (95% CI 0.64 to 1.18)
					Stroke	RR = 1.04 (95% CI 0.92 to 1.17)
					Heart failure	RR = 0.90 (95% CI 0.76 to 1.07)
					Angina	RR = 0.80 (95% CI 0.58 to 1.11)
					Revascularisation	RR = 0.97 (95% CI 0.77 to 1.22)
					ESRD	RR = 0.99 (95% CI 0.78 to 1.28)
					Major adverse CV events	RR = 0.97 (95%CI 0.89 to 1.06)
					Drug withdrawal owing to adverse events	RR = 0.80 (95% CI 0.61 to 1.05)

* Only three trials enrolled patients with microalbuminuria or proteinuria
** 14 trials compared RAS blockers with a calcium channel blocker, three with a thiazide diuretic, and two with a betablocker. In 14 trials the RAS blockers were an ACE inhibitor and in 5 an ARB

Comparaison antihypertenseurs chez diabétiques

majoritairement +HTA et sans protéinurie – Bangalore 2016

Death	No of events/total RAS	No of events/total Control	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
RAS *v* calcium channel blocker					
ABCD (hypertensive)	14/235	18/235		0.77	0.78 (0.39 to 1.56)
ABCD (normotensive)	19/181	19/173		0.93	0.96 (0.51 to1.81)
ALLHAT (diabetes mellitus)	674/3510	683/3597		33.04	1.01 (0.91 to1.13)
ALLHAT (impaired fasting glucos)	58/407	55/364		2.75	0.94 (0.65 to 1.36)
BENEDICT	3/301	2/303		0.12	1.51 (0.25 to 9.04)
CASE-J	40/586	49/609		2.15	0.85 (0.56 to 1.29)
FACET	4/189	5/191		0.22	0.81 (0.22 to 3.01)
Fogari et al	3/103	4/102		0.17	0.74 (0.17 to 3.32)
IDNT	87/579	83/567		4.14	1.03 (0.76 to 1.39)
JMIC-B	5/173	2/199		0.14	2.88 (0.56 to 14.82)
MITEC	0/100	0/109		0.02	1.09 (0.02 to 54.93)
NAGOYA HEART	22/575	16/575		0.90	1.38 (0.72 to 2.62)
STOP-2	56/235	50/231		2.57	1.10 (0.75 to 1.61)
D+L Subtotal: P=0.973, I^2=0%				47.91	1.01 (0.92 to 1.10)
I-V Subtotal					1.01 (0.92 to 1.10)
RAS *v* diuretic					
ALLHAT (diabetes mellitus)	674/3510	1145/5994		41.33	1.01 (0.91 to 1.11)
ALLHAT (impaired fasting glucose)	58/407	107/628		3.66	0.84 (0.61 to 1.15)
NESTOR	1/286	2/283		0.06	0.50 (0.05 to 5.46)
D+L Subtotal: P=0.475, I^2=0%				45.05	0.99 (0.90 to 1.08)
I-V Subtotal					0.99 (0.90 to 1.08)
RAS *v* β blocker					
LIFE (diabetes mellitus)	63/586	104/609		3.82	0.63 (0.46 to 0.86)
UKPDS 39	75/400	59/358		3.22	1.14 (0.81 to 1.60)
D+L Subtotal: P=0.012, I^2=84.1%				7.04	0.84 (0.47 to 1.51)
I-V Subtotal					0.83 (0.66 to 1.04)
D+L Overall: P=0.611, I^2=0%				100.00	0.99 (0.93 to 1.05)
I-V Overall					0.99 (0.93 to 1.05)

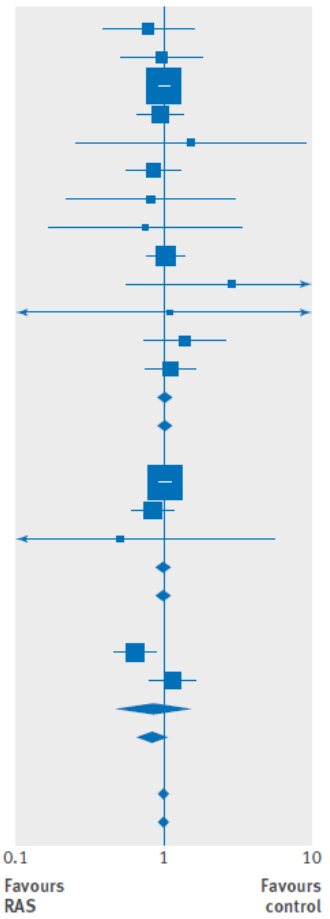

Fig 1 | Outcomes of death with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

Comparaison antihypertenseurs chez diabétiques

majoritairement +HTA et sans protéinurie – Bangalore 2016

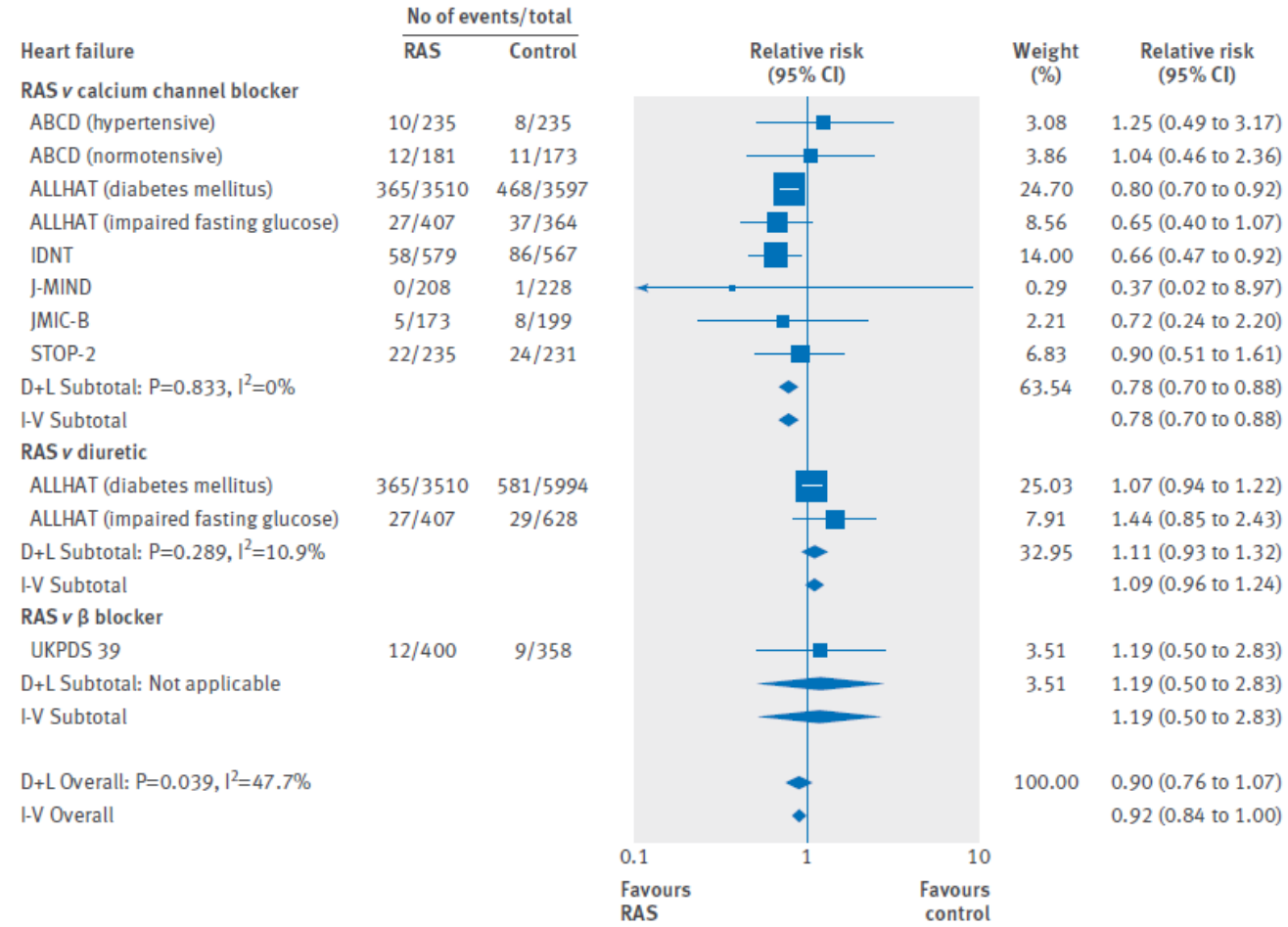

Fig 6 | Outcome of heart failure with renin angiotensin system (RAS) blockers compared with other antihypertensives in people with diabetes

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Débuter IEC/sartans – Sécurité

Avant initiation du traitement	• Kaliémie + eDFG • Contre-indications - Hyperkaliémie - Sténose bilatérale des artères rénales ou sténose sur rein unique - Grossesse
En début de traitement	• Possibilité d'insuffisance rénale aiguë → débuter par de (très) faible dose si déplétion volémique, personne âgée, insuffisance cardiaque, insuffisance rénale, artériopathie périphérique ou athérosclérose généralisée
En cours de traitement	• Kaliémie – eDFG 2 sem après début de traitement, et après chaque ↗ posologie • Interactions pharmacodynamiques - Insuffisance rénale, hyperkaliémie, hyponatrémie, hypoglycémie, hypotension artérielle,… - ↘ élimination rénale de la digoxine, du lithium,…

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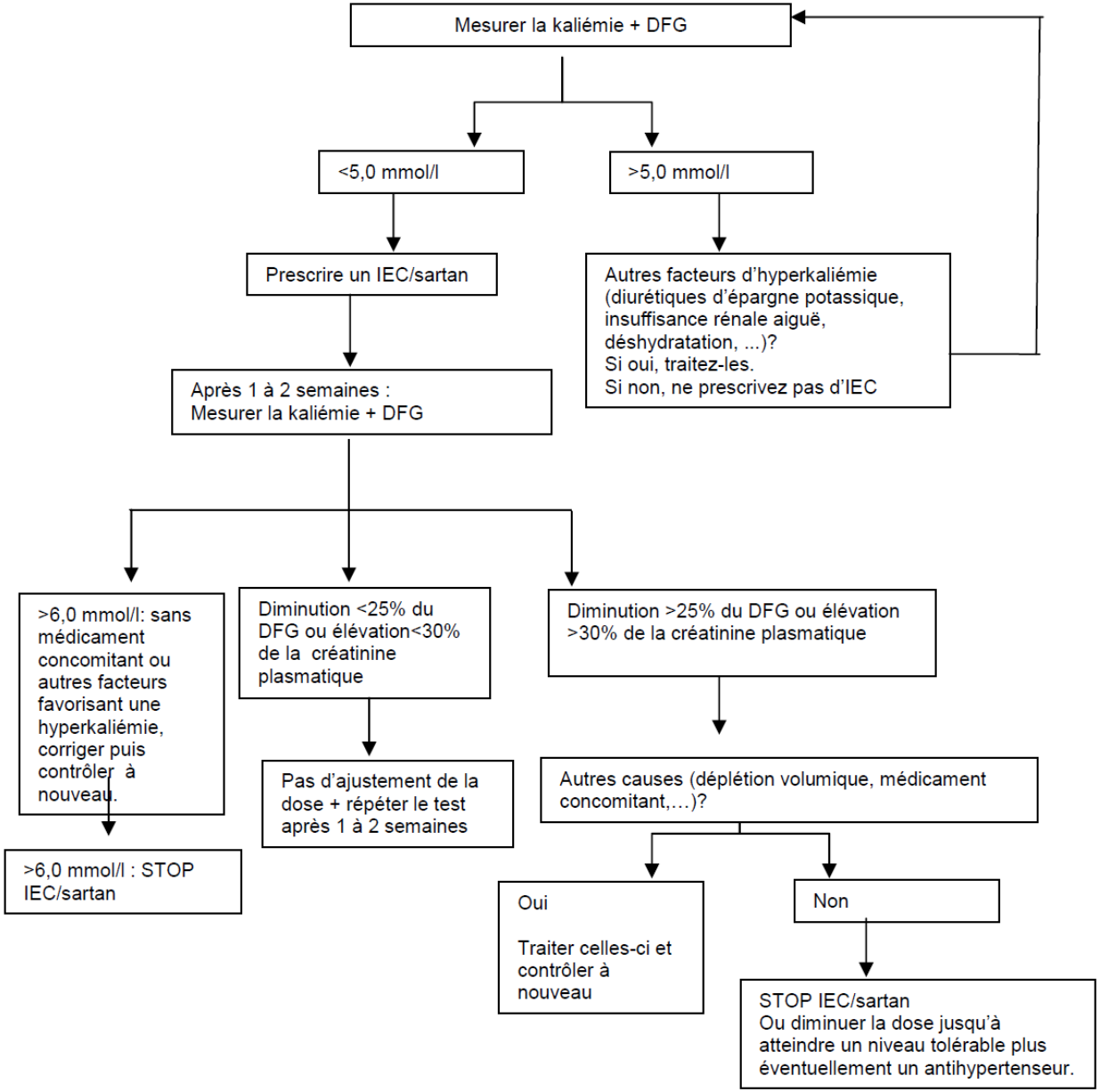
CBIP RCM 2015, Prescrire Le Guide 2015, SSMG 2012

Débuter IEC/sartan : organigramme



IEC/Sartans – Sécurité

Effets indésirables	• Hypotension artérielle • Sensation vertigineuse, fatigue, céphalées, paresthésies • Troubles digestifs; Entéropathie chronique avec diarrhée sous olmésartan • Hyperkaliémie, hyponatrémie • Insuffisance rénale • Atteintes cutanées, photosensibilité • Angiœdème • Toux (surtout IEC) • Hypoglycémie • Troubles du goût • Crampes • Rares neutropénie, agranulocytose, thrombopénie, anémie • Rares stomatite, pancréatites, atteintes hépatiques • Mortalité cardiovasculaire chez diabétique de type 2 sous olmésartan • Fœtaux
Précautions d'utilisation	• Hypotension lors de la 1ère prise si déplétion volémique → débuter par très faible dose (p. ex. 1/4) et augmenter progressivement • Débuter avec faible dose et augmenter progressivement, surtout si personne âgée ou IC ou IR • Contrôler fonction rénale lors de l'instauration du traitement et environ deux semaines plus tard • Débuter prudemment en cas d'artériopathie périphérique ou d'athérosclérose généralisée en raison du risque élevé de sténose des artères rénales chez ces patients
Contre-indications	• Grossesse • Sténose bilatérale des artères rénales ou sténose sur rein unique • Hyperkaliémie

IEC/Sartans – Sécurité

Interactions	Addition de risque d'**IR fonctionnelle**	• AINS si hypovolémie, déshydratation, IC, sténose de l'artère rénale • Diurétiques (via hypovolémie) • IEC, sartans, aliskirène		
	Addition d'effet **hyponatrémiant**	• Diurétiques thiazidiques et apparentés, acétazolamide • Desmopressine • SSRI, SNRI, agomélatine • Des antiépileptiques: carbamazépine, oxcarbazépine, lamotrigine, lévétiracétam • Sulfamidés hypoglycémiants		
	Addition d'effet **hyperkaliémiant**	• Sels de potassium • Diurétiques d'épargne potassique • IEC, sartans, aliskirène • Digoxine, surtout en cas de surdose	• Héparines • Epoétines • AINS	• Drospirénone • Triméthoprime • Pentamidine
	Addition d'effet **hypoglycémiant**	• Médicaments du diabète • Des antiarythmiques: cibenzoline, disopyramide, quinidine		
	Aggravation d'**angiœdème** liés à certains médicaments, désensibilisation par venin d'hyménoptère			
	Addition de risque de **crampes**	• Via troubles électrolytiques : diurétiques, laxatifs, corticoïdes • Médicaments exposant aux crampes		
	Addition de risque d'**anémie et d'agranulocytose** : azathioprine			
	Addition (antihypertenseur) ou antagonisme (pseudoephedrine,…) d'effet sur la **pression artérielle**			
	Antagonismes d'effet : époïétines			
	↘ élimination rénale de…	• Lithium, digoxine, metformine, des antiarythmiques (cibenzoline, disopyramide, flécaïnide, sotalol, quinidine, propafénone, méxilétine), fibrates		
	Autres	• Inhibiteurs du 2C9 : accumulation de l'irbésartan, ↘ possible de l'effet du losartan • Sels d'or		

Listes non-exhaustives

CBIP RCM 2015, Prescrire Le Guide 2015

Statines vs placebo chez diabétiques
sans antécédent coronarien

Costa 2006						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*Patients with diabetes mellitus Mean age 47-75y* *Primary coronary artery disease prevention* *Mainly with 1 or more CVRF*	5/10703	Mean weighted FU 4.5 y	Statin vs Placebo	Major coronary events* (I)	**8% vs 10.1%**** **RR = 0.80 (95%CI 0.71 to 0.90)** **NNT = 37/4.5y*****

* Defined as coronary artery disease death, non-fatal myocardial infarction, or myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty).
** The absolute risk numbers are calculated from the tables in the publication : number of events in the group of diabetic patients with "any statin" treatment versus number of events in the group of diabetic patients with placebo treatment.
*** The NNT numbers are from the publication with the following explanation : "We calculated the number needed to treat and 95% confidence interval from meta-analysis estimates (adjusted odds ratio) and did not treat the data as if they all arose from a single trial, as this approach is more prone to bias, especially when important imbalances exist between groups within one or more trials in the meta-analysis"

Statines vs placebo chez diabétiques
sans maladie vasculaire

Kearney 2008 (CTT)						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*Patients with diabetes mellitus Mean age 63.1y* *Without vascular disease*	14/18686 (I and II prevention together **)	Mean FU 4.3 y	Statin vs Placebo	Major vascular events* (I)	**9.2% vs 11.8%** **RR = 0.73 (95%CI 0.66 to 0.82)** **(per mmol/L LDL cholesterol reduction***)**

* The primary meta-analyses (Baigent 2005 : Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins) were of the effects on clinical outcomes with each trial weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of follow-up, and were reported as the effects per 1·0 mmol/L reduction in LDL cholesterol. Since many fewer outcomes were available for analysis in individuals with diabetes, we examined possible variation in the proportional effects of allocation to a statin in different circumstances only for major vascular events.

** CTT evaluated together people with and without CV history, the subgroup analysis were made from the number of events, so we don't know how many diabetic patients were in the primary prevention group . In the original publication (Baigent 2005), there were 90056 patients (in which 18686 diabetes patients). We know that in the global group of 90056, 41354 were without history of CVD (46%), so 48702 (54%) were with a history of CVD. In the present publication (Kearney 2008), we only have the number of events by subgroup of primary or secondary prevention analysis.

*** LDL : 1 mmol/l = +/- 40 mg/dl

Statines vs placebo chez diabétiques
avec antécédent coronaire

Costa 2006						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*Patients with diabetes mellitus* *Mean age 47-75y* *With previous coronary heart disease*	7/4672	Mean weighted FU 5.1 y	Statin vs Placebo	Major coronary events* (I)	**27.5% vs 33.5%**** **RR = 0.79 (95%CI 0.68 to 0.93)** **NNT = 15/5.1y*****
		3/902	Mean weighted FU 5.0 y		Coronary heart disease death (II)	**9.5% vs 11.5%**** **RR = 0.83 (95%CI 0.57 to 1.21)** **NNT = 19/5.0y*****

* defined as coronary artery disease death, non-fatal myocardial infarction, or myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty).
** The absolute risk numbers are calculated from the tables in the publication : number of events in the group of diabetic patients with "any statin" treatment versus number of events in the group of diabetic patients with placebo treatment.
*** the NNT numbers are from the publication with the following explanation : "We calculated the number needed to treat and 95% confidence interval from meta-analysis estimates (adjusted odds ratio) and did not treat the data as if they all arose from a single trial, as this approach is more prone to bias, especially when important imbalances exist between groups within one or more trials in the meta-analysis"

Statines vs placebo chez diabétiques
avec maladie vasculaire

Kearney 2008 (CTT)						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*Patients with diabetes mellitus Mean age 63.1y* *With vascular disease*	14/18686 (I and II prevention together **)	Mean FU 4.3 y	Statin vs Placebo	Major vascular events* (I)	**26.3% vs 31.6%** **RR = 0.80 (95%CI 0.74 to 0.88) (per mmol/L LDL cholesterol reduction)** **NNT = 19/4.3y**

*The primary meta-analyses (Baigent 2005 : Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins) were of the effects on clinical outcomes with each trial weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of follow-up, and were reported as the effects per 1·0 mmol/L reduction in LDL cholesterol. Since many fewer outcomes were available for analysis in individuals with diabetes, we examined possible variation in the proportional effects of allocation to a statin in different circumstances only for major vascular events.

** CTT evaluated together people with and without CV history, the subgroup analysis were made from the number of events, so we don't know how many diabetic patients were in the primary prevention group . In the original publication (Baigent 2005), there were 90056 patients (in which 18686 diabetes patients). We know that in the global group of 90056, 41354 were without history of CVD (46%), so 48702 (54%) were with a history of CVD. In the present publication (Kearney 2008), we only have the number of events by subgroup of primary or secondary prevention analysis.

*** LDL : 1 mmol/l = +/- 40 mg/dl

Statines vs placebo chez diabétiques

groupe mixte : avec et sans maladie vasculaire - mortalité

Kearney 2008 (CTT)						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*patients with diabetes mellitus Mean age 63.1y Mixed with and without vascular disease*	14/18686	mean FU 4.3 y	Statin vs Placebo	All cause mortality	**RR = 0.91 (99% CI 0.82–1.01)** p = 0.02**
					Mortality due to coronary heart disease	**RR = 0.88 (99% CI 0.75–1.03)** p = 0·03**
					All- vascular mortality	**RR = 0.87 (99% CI 0.76–1.00)** p = 0·008**

The primary meta-analyses (Baigent 2005 : Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins) were of the effects on clinical outcomes with each trial weighted by the absolute LDL cholesterol difference in that trial at the end of the first year of follow-up, and were reported as the effects per 1·0 mmol/L reduction in LDL cholesterol. Since many fewer outcomes were available for analysis in individuals with diabetes, we examined possible variation in the proportional effects of allocation to a statin in different circumstances only for major vascular events.

** This study represents 99% confidence intervals in stead of 95% CI. When considering p<0,05 as statistically significant, this results are SS.

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Statines : puissantes versus moins puissantes
pas chez patients diabétiques

Tonelli 2011						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*Primary CV prevention in low risk population** *(Diabetes patients excluded)*	29/80711	0.5 to 5.3 y mean FU 2y	High potency vs Low potency statin (indirect comparisons)**	All cause mortality	NS RR = 0.94 (95%CI 0.79 to 1.13)
					MI (fatal or not)	NS RR = 0.69 (95%CI 0.43 to 1.12)
					Stroke	NS RR = 0.79 (95%CI 0.61 to 1.02)

* : We defined low risk as an observed 10-year risk of less than 20% for cardiovascular-related death or nonfatal myocardial infarction
** : Meta-analysis was designed for the comparison of statin versus placebo. The comparison between high potency versus low potency statin was a subgroup analyses by indirect comparisons. High potency statins were atorvasatatin and rosuvastatin. Low potency statins were fluvastatin, lovastatin, pravastatin and simvastatin

Statines : hautes vs faibles doses chez diabétiques
avec maladie coronaire

Sheperd 2006 (TNT study)						
Design	Population	n	Duration	Intervention	Outcome	Result
RCT	*Diabetes* *Previous CHD (MI, angina, obvious coronaropathy, previous revascularisation procedure)* *35-75 y* *LDL<130mg/dl*	1501	5 y	Atorvastatin 80mg/d vs Atorvastatin 10mg/d	First major CV event* (I)	**HR = 0.75 (95%CI 0.58 to 0.97)** **13.8 % vs 17.9 %** **NNT = 24/5y**
					All-cause mortality (II)	NS 10.8 % vs 9.8%
					Any CV event (II)	NS (Trend) HR = 0.85 (95%CI 0.73 to 1.00) 39.8% vs 44.1%
					Major coronary event** (II)	NS
					Any coronary event (II)	NS
					Cerebrovascular event (II)	**HR = 0.69 (95%CI 0.48 to 0.98)** **7% vs 10%**
					Peripheral arterial disease (II)	NS
					Hopitalization for CHF (II)	NS
					Treatment related AE***	7% vs 5.4% NS

- Major exclusion criteria included statin hypersensitivity, current liver disease, nephrosis, pregnancy or uncontrolled CHD risk factors, CHD event or revascularization within less than a month, congestive heart failure, unexplained creatine phosphokinase levels more than six times the upper limit of normal, life-threatening malignancy, or immunosuppressive or lipid-lowering drug treatment.

*death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke

**CHD death, nonfatal non–procedure-related myocardial infarction, or resuscitated cardiac arrest

***Treatment-related adverse events, including myalgia, or persistent elevations in liver enzymes. No incidents of rhabdomyolysis were reported in either treatment group with diabetes

Statines : “treat to target” vs “fire and forget”

Presenting feature	Simvastatin-allocated	Placebo-allocated	Event rate ratio (95% CI)	Heterogeneity or trend χ^2
Prerandomisation LDL response				
Smaller (<38%)	700/3516 (19·9%)	911/3558(25·6%)		0·08
Average	649/3252 (20·0%)	822/3272(25·1%)		
Larger (≥48%)	684/3501 (19·5%)	852/3437(24·8%)		
ALL PATIENTS	**2033/10 269(19·8%)**	**2585/10 267(25·2%)**	**0·76 (0·72–0·81) p<0·0001**	

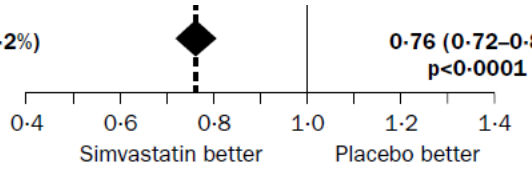

Figure 8: **Effects of simvastatin allocation on first major vascular event in different categories of participant**
Symbols and conventions as in figure 2. χ^2 tests on one degree of freedom are given for heterogeneity between rate ratios within dichotomous categories and for trend within other categories (with value >3·84 equivalent to p<0·05 before making allowance for multiple comparisons). Lipid categories relate to measured values at the initial screening visit prior to starting any statin therapy. Prerandomisation “LDL response” relates to percent reduction in measured LDL cholesterol between the screening and randomisation clinic visits following 4–6 weeks of 40 mg simvastatin daily “run-in” treatment, which was provided to all patients (irrespective of their subsequent random allocation). Treatment for hypertension and other treatments recorded at entry to the study generally continued during follow-up (as did the vitamins allocated in the 2×2 factorial design[24]). *Slightly elevated creatinine defined as ≥110 μmol/L for women and ≥130 μmol/L for men, but <200 μmol/L for both.

In the HPS, all participants received 40 mg of simvastatin (the study drug) before randomization and investigators measured each participant’s biological response to statin therapy. This allowed to match control and intervention participants according to their response to statin therapy (during this run-in phase). Contrary to the LDL log-linear hypothesis (which would suggest that those who have a larger LDL cholesterol response from a given statin dose would receive greater benefit), **those with the worst prerandomization LDL response (<38% reduction in LDL cholesterol level) received the same benefit as those with the best LDL response (≥47% reduction in LDL cholesterol level**)

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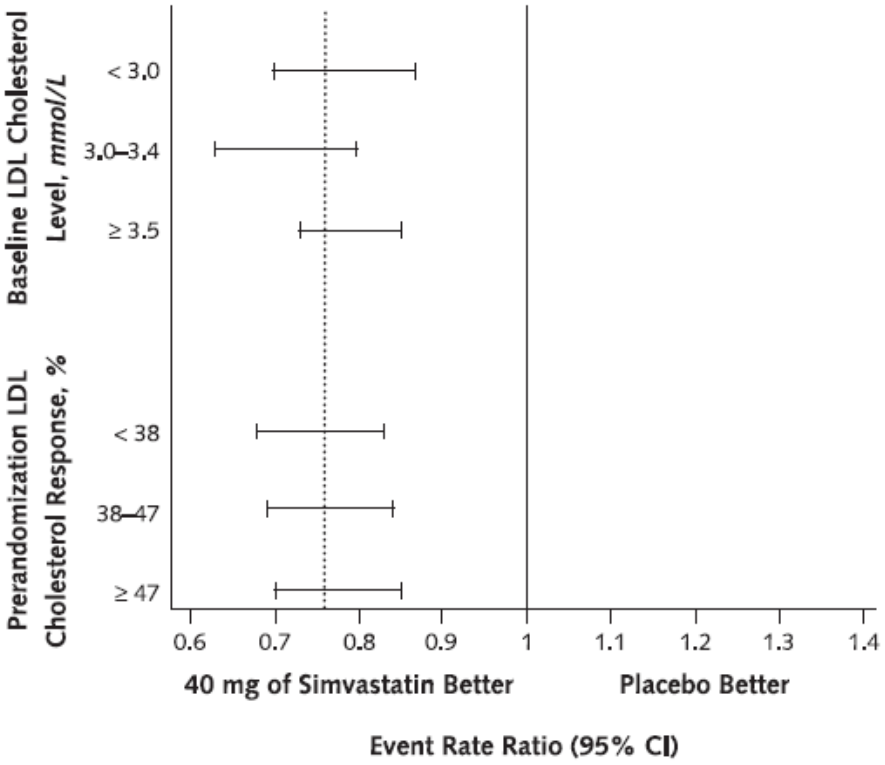
Collins 2002

Statines : “treat to target” vs “fire and forget”

Figure 2. **Results for the Heart Protection Study.**



No statistically or clinically significant difference was seen in relative benefit of statin therapy by low-density lipoprotein (*LDL*) cholesterol level at baseline or prerandomization LDL response. To convert LDL cholesterol values to mg/dL, divide by 0.02586.

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Hayward 2006

Levure de riz rouge

Données insuffisantes
Si indication R/ médicamenteux : préférer une statine enregistrée

Contient notamment de la monacoline K (= lovastatine)

- **Efficacité**
  - Complément alimentaire (concentration monacoline K très variable)
  - 1 RCT prévention secondaire (ATCD IM) : ↘ morbidité CV
  - Peu de données sur l'efficacité dans le diabète de type 2
- **Sécurité**
  - Peu de données à long terme
  - Statine →Toxicité musculaire non-exclue, association statine déconseillée
  - Complément alimentaire (citrinine – néphrotoxique chez animal)

Pas d'avis dans les guidelines consultés

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Gordon 2010, ESC 2011, NICE 2010

Statines – Effets indésirables

Troubles digestifs (fréquent)
Céphalées, vision trouble, sensations vertigineuses, insomnie, dysgeusie
↗ CPK, crampes, atteintes musculaires, rhabdomyolyse Tendinites
↗ transaminases, hépatite (rare)
Diabète
Pancréatite, polyneuropathie périphérique, pneumopathie interstitielle, fibrose pulmonaire (rares)
Réaction d'hypersensibilité

Statines – Facteurs de risque musculaire

- Femme
- Petite taille et faible poids
- Âge avancé
- Alcoolisme
- Dose élevée de statine

- Dysfonction rénale
- Dysfonction hépatique
- Période péri-opératoire
- Hypothyroïdie
- Pathologie musculaire préexistante

Interactions médicamenteuses pharmacodynamiques		**Pharmacocinétiques**
Crampes : surtout via troubles hydroélectrolytiques	Rhabdomyolyse	
• des médicaments CV : diurétiques, IEC, sartans, bêtabloquants, ivabradine, nifédipine, fibrates • les bêta-2 mimétiques • des laxatifs • des antiparkinsoniens (bromocryptine, tolcapone) • les corticoïdes • les hormones thyroïdiennes • les modulateurs sélectifs des récepteurs aux estrogènes • des antiestrogènes (tamoxifène, …) • des cytotoxiques • le ranélate de strontium • des immunosuppresseurs • des hypoglycémiants (glitazones, …)	• des hypolipémiants : fibrates, ézétimibe • des neuroléptiques • des amphétaminiques (bupropion, …) • la colchicine • des antipaludiques (hydroxychloroquine, chloroquine) • le ranélate de strontium • les corticoïdes • des médicaments entraînant des troubles hydroélectrolytiques (diurétiques, laxatifs, …) • naltrexone • des antirétroviraux, immunosuppresseurs (ciclosporine, tacrolimus), un anticancéreux (temsirolimus)	• Inhibiteurs du P450

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Prescrire 2012, ESC/EAS 2011 CBIP 2013

Statines - Interactions

Médicaments entraînant des crampes musculaires

Médicaments exposant aux atteintes musculaires

Inhibiteurs 3A4 : ↗ effet simvastatine et atorvastatine

- macrolides (**clarithromycine**, **érythromycine, télithromycine**)
- antifongiques azolés (fluconazole, **itraconazole**, **kétoconazole, posaconazole, voriconazole**)
- **pamplemousse/pomélo**
- médicaments CV (amiodarone, **diltiazem,** nicardipine, **vérapamil**)
- SSRI (fluoxétine, fluvoxamine)
- linagliptine
- des antiviraux et antirétroviraux

Inhibiteurs 2C9 : ↗ effet fluvastatine (rosuvastatine partiellement métabolisée par 2C9)

- **voriconazole**
- SSRI (fluoxétine, **fluvoxamine**)
- anti-H2 (cimétidine)
- ticlopidine
- topiramate

AVK : ↗ INR et risque de saignements, avec toutes les statines

Les inhibiteurs puissants sont mentionnés en caractère gras

Influence du risque initial ?

Par exemple, chez 10 000 patients, si pour un événement : RR = 0,8

→ 20% de réduction du risque

- Si risque CV faible (1%/10 ans)
  - Après 10 ans sans statine : 100 nouveaux cas
  - Avec statine : 20 cas sont prévenus (= RAR)
  - NNT 500 sur une durée de 10 ans
- Si risque élevé (10%/10 ans)
  - Après 10 ans sans statine : 1000 nouveaux cas
  - Avec statine : 200 cas sont prévenus (= RAR)
  - NNT 50 sur une durée de 10 ans

Statines: Quelle statine/ quelle dose ? - GPC

- **NICE:**
  - Atorvastatine 20mg sans antécédents CV
  - Atorvastatine 80 mg si antécédent CV

- **ADA:**

Age	Risk factors	Recommended statin dose*
<40 years	None	None
	CVD risk factor(s)**	Moderate or high
	Overt CVD***	High
40–75 years	None	Moderate
	CVD risk factors	High
	Overt CVD	High
>75 years	None	Moderate
	CVD risk factors	Moderate or high
	Overt CVD	High

NB : “Moderate” et “high” ne sont pas spécifiés et aucune statine n’est privilégiée

- **Domus Medica:** Aucune statine ou dose ne sont privilégiées

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ADA 2015, NICE 2015, Domus Medica 2015

Statines: Quelle statine/ quelle dose ? - GPC

- ADA ne précise pas ce que sont les “High/Moderate Statine”
- Vriasemblablement basé sur la classification des statines par l’ACC-AHA:

Table 5 High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mgRosuvastatin 20 (40) mg	Atorvastatin 10 (20) mgRosuvastatin (5) 10 mgSimvastatin 20–40 mg‡Pravastatin 40 (80) mgLovastatin 40 mgFluvastatin XL 80 mgFluvastatin 40 mg BIDPitavastatin 2–4 mg	Simvastatin 10 mgPravastatin 10–20 mgLovastatin 20 mgFluvastatin 20–40 mgPitavastatin 1 mg

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study (47).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.
Boldface type indicates specific statins and doses that were evaluated in RCTs (16–18,46–49,64–75,77) included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.BID indicates twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

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ACC-AHA 2014

AAS chez diabétiques sans antécédents CV

De Berardis 2009						
Design	Population	Intervention	N/n	Duration	Endpoints	Results
MA of RCTs	*Diabetes, No pre-existing cardiovascular disease*	ASA vs Placebo or no treatment	5/9584	3.6 to 10.1y	Major cv events	RR = 0.90(95%CI 0.81-1.00) NS
			4/8557		Cardiovascular mortality	RR = 0.94(95%CI 0.72-1.23) NS
			3/6018		All cause mortality	RR = 0.93 (95%CI 0.82-1.05) NS

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De Berardis 2009

AAS en prévention secondaire

Baigent 2009 (ATT collaboration)						
Design	Population	N/n	Duration	Intervention	Outcome	Result
SR +/- MA of RCT's	*individuals with previous MI or stroke or transient cerebral Ischaemia*	16/17029 (+/_ 1749 with diabetes)	From 3,7 and 10 y	Aspirin (75 -500mg/d) vs Placebo or no treatment	Serious vascular event (I)	**RR = 0.81 (95%CI 0.75 to 0.87)** **6.7% vs 8.2%/y** **NNT = 67/y**
					Major coronary event (I)	**RR = 0.80 (95%CI 0.73 to 0.88)** **4.3% vs 5.3%/y** **NNT = 100/y**
					Any stroke (I)	**RR = 0.81 (95%CI 0.71 to 0.92)** **2·08% vs 2·54%/y** **NNT = 217/y**
					Vascular death (II)	RR = 0.91 (95%CI 0.82 to 1.00)
					Major extracranial bleed (I)	**RR = 2.69 (95%CI 1.25 to 5.76)** **0.25% vs 0.06%/y** **NNH = 526/y**

- The main outcomes were serious vascular event, defined as myocardial infarction, stroke, or death from a vascular cause (including sudden death, pulmonary embolism, haemorrhage, and, for secondary prevention trials only, death from an unknown cause); major coronary event (myocardial infarction, coronary death, or sudden death); any stroke (haemorrhagic or probably ischaemic [ie, defi nitely ischaemic or of unknown type]); death from any cause; and major extracranial bleed (mainly gastrointestinal and usually defined as a bleed requiring transfusion or resulting in death).

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Baigent 2009

The end

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