Risque rénal du patient vasculaire et risque cardiovasculaire du patient rénal

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DIU Hypertension artérielle
8 novembre 2018

Epidémiologie
et épidémiologie clinique

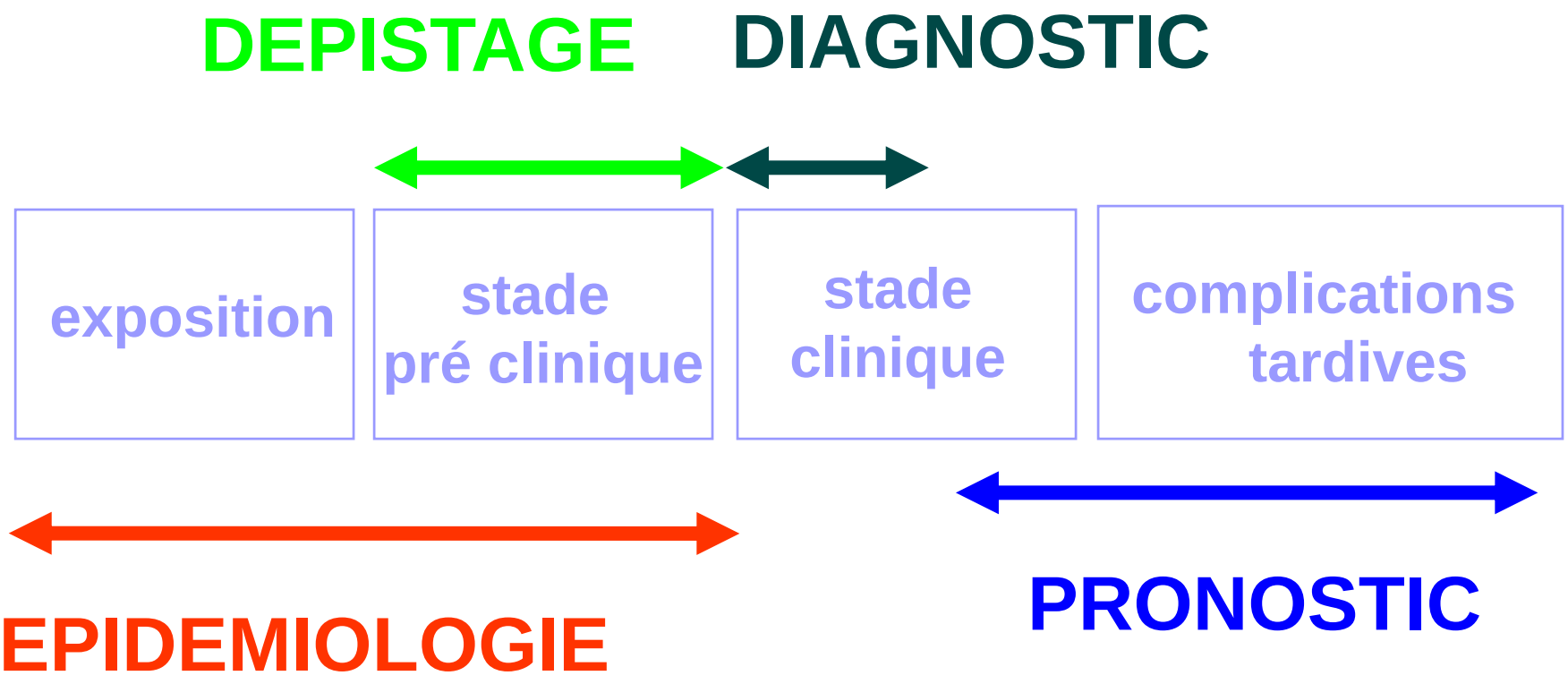
L'épidémiologie concerne l'étude de la distribution des états de santé dans les populations humaines et de leurs déterminants.

L'épidémiologie clinique est l'application des principes et méthodes de l'épidémiologie pour conduire, évaluer ou réaliser des études de recherche clinique en prévention, diagnostic, pronostic ou traitement des maladies.

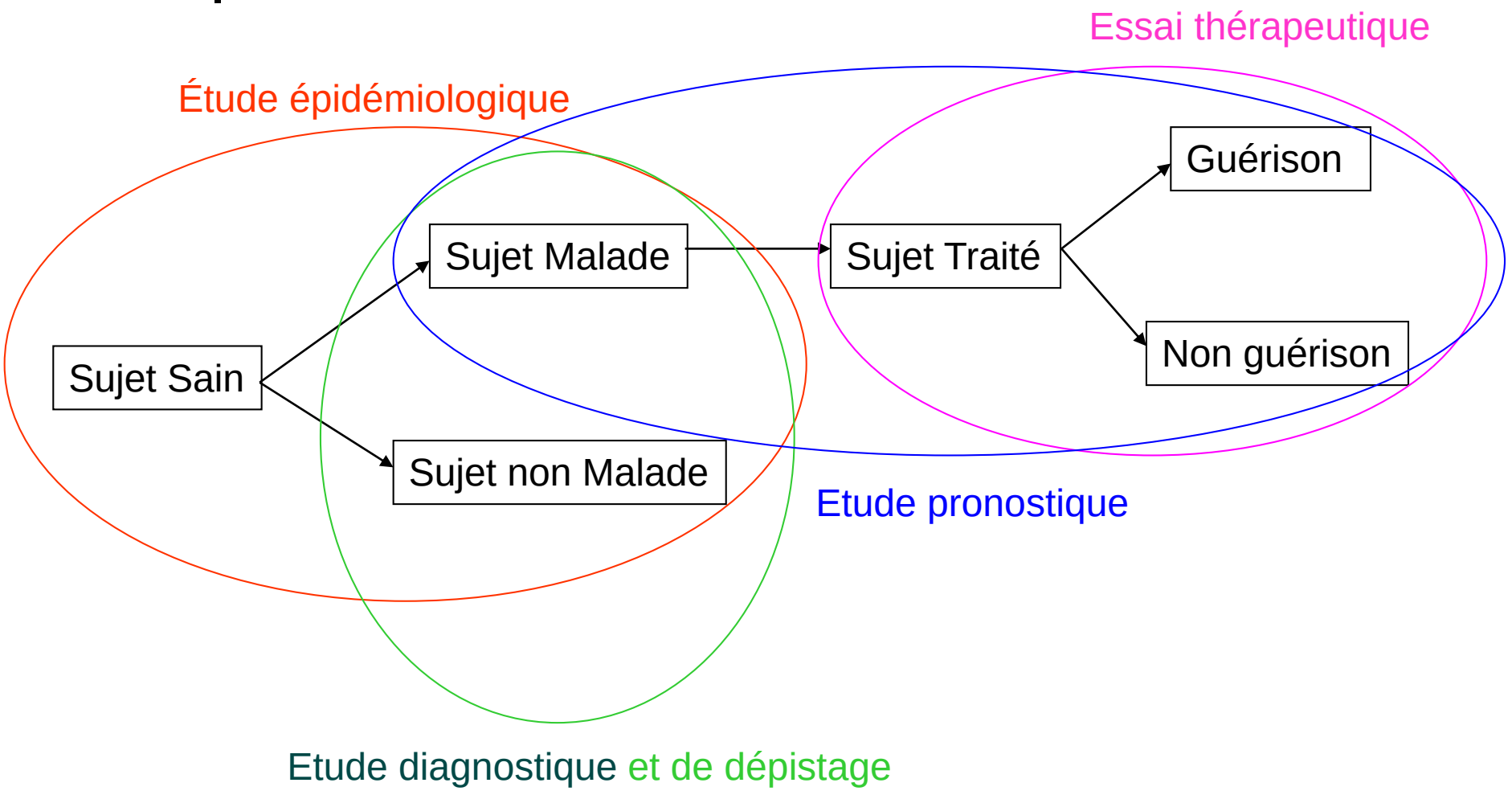
Science fondamentale de l'Evidence-based Medicine

Mac Mahon B, Pugh TF. Epidemiology, principles and methods.
Boston, Little, Brown publ., 1970.

Approche de l'histoire naturelle de la MRC



Types d'études



Studies and surveys

classification according to :

- I - Time
  - Cross sectional
  - longitudinal
- II - Subjects
  - Complete
  - sampling
- III - Objectives
  - Descriptive survey
  - Analytical survey
- IV - Procedure
  - Experimental
  - Observational

Surveys according to objectives

- Descriptive survey
- Analytical
  - Etiological
  - Evaluative

Analytical surveys

- Etiological surveys

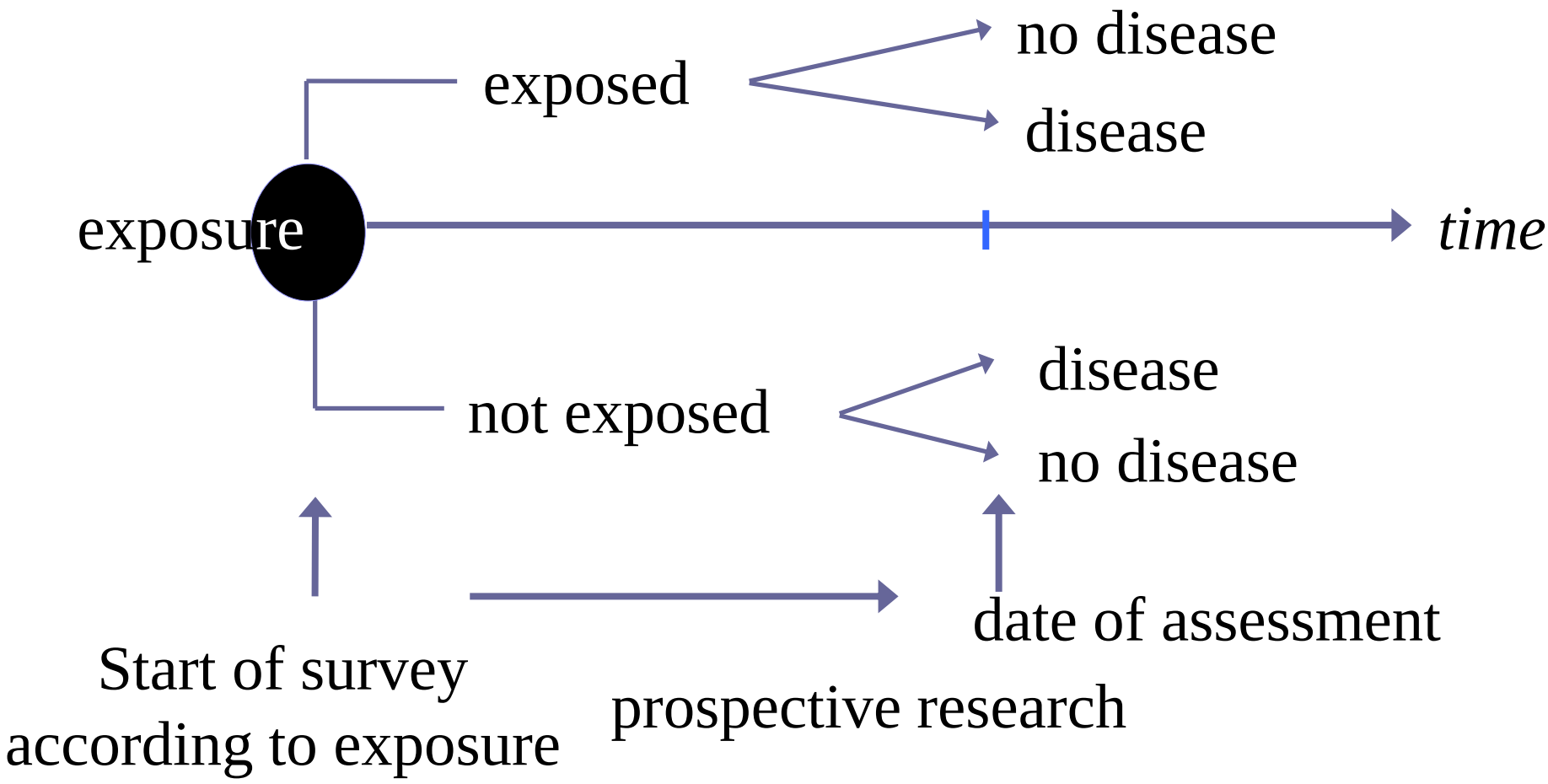
Aim: looking for a link of causality between a given factor and a disease

Means:

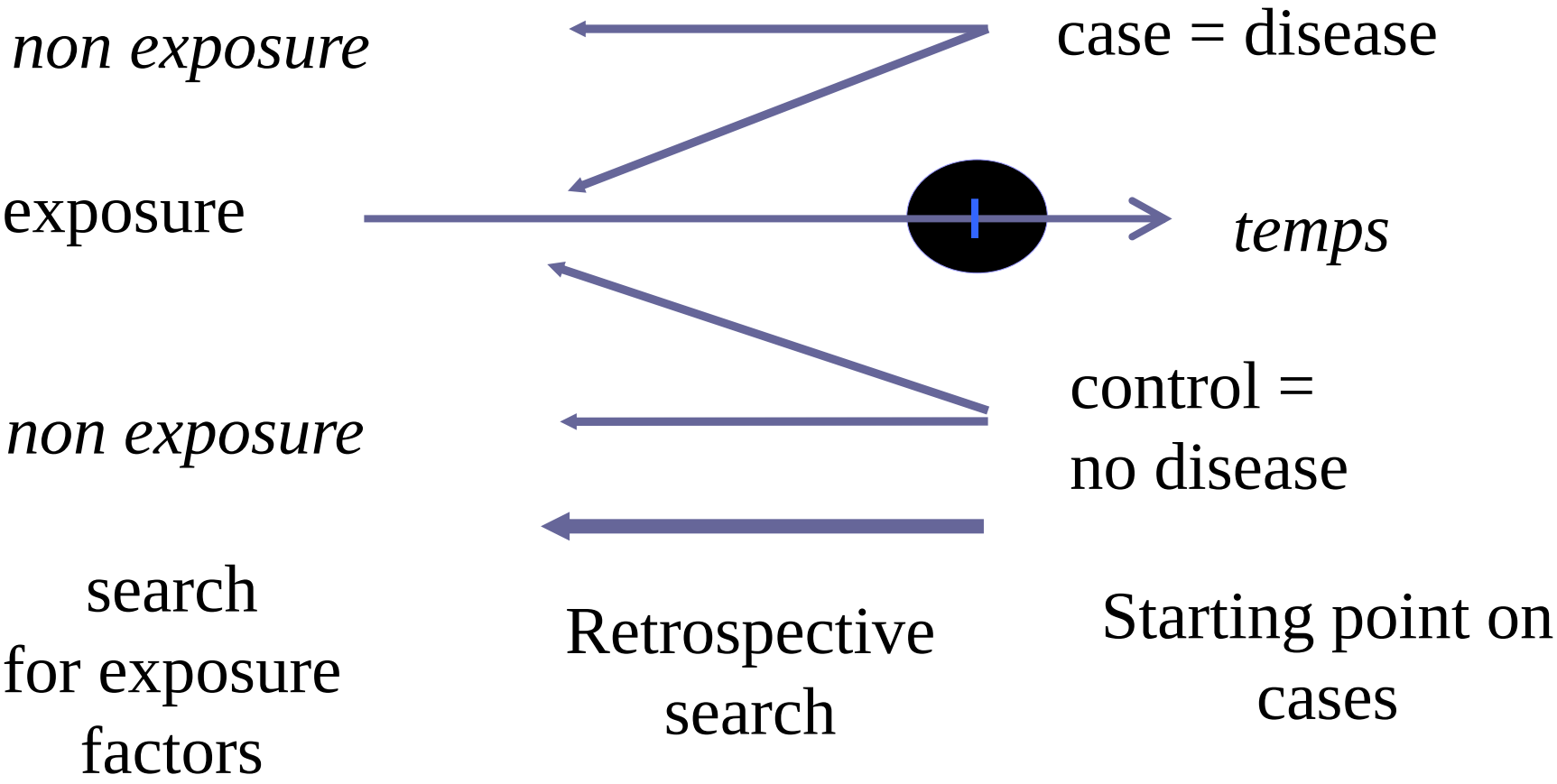
prospective

or retrospective surveys

Prospective survey exposed - non exposed



Retrospective survey case - control



Enquête épidémiologique et étude pronostique : parentés et différences

- Enquête épidémiologique à visée étiologique
  - Population de sujets sans MRC au départ (en théorie)
  - Recherche de facteurs de risque intrinsèques ou environnementaux de développer la MRC
  - Facteur temporel
  - État final étudié : survenue de la MRC
  - Les facteurs de risque ou d'exposition peuvent dans certains cas être contrôlés (étude d'intervention)
- Etude pronostique
  - Population de patients ayant une MRC
  - Etude de la performance de facteurs pronostiques à discriminer entre les différentes évolutions possibles de la MRC
  - Facteur temporel
  - Etat final étudié : guérir, améliorer, stabiliser ou simplement retarder
  - Pas de possibilité de contrôler en général les facteurs pronostiques étudiés

Work flow d'un projet de recherche clinique

Demande clinicien/
Fiche de démarrage

Rédaction du protocole/évaluation financière

Conception du CRF (papier)

PROTOCOLE et faisabilité

ANALYSE VALORISATION

Rédaction article…

Rapport d'étude

Analyse statistique

Data management

Fin de suivi étude

Cahier des charges Data management
fin des inclusions

Pendant l'étude
- Inclusion, suivi patients
- Saisie des données
- Logistique
- EIG
- DSMB
- Modification substantielle
- Problème randomisation
- Problème e-CRF

1ère inclusion

Dossiers pour accords règlementaires

Début conventions

Amendements CPP

TECHNICO REGLEMENTAIRE

TERRAIN

Cahier des charges Data monitoring:
- Choix variables à monitorer

Mise en place des OUTILS et PROCEDURES

Conception e-CRF Randomisation

Cahier des charges TEC:
- Convention de saisie
- Guide de remplissage

Tests

Validation e-CRF

Signature conventions

Risque rénal

- Si 11.029 nouveaux cas d'insuffisance rénale terminale (IRT) sont survenus au cours de l'année 2016, en France, alors le risque estimé d'IRT est de 165 pmp.
- Ce résultat suppose que le risque d'IRT est analogue pour chacun,
- ce n'est bien sur pas le cas.

Facteurs de risque rénal

- Pour un sujet donné, plusieurs facteurs peuvent contribuer à augmenter le risque de MRC.
- Si une relation existe entre un FdR et la MRC, alors on peut explorer son **intensité** comme une fonction de la *dose* et de la *durée* de l'exposition.
- Une mesure matérialise le degré de la relation entre FdR et MRC : un *excès de risque*, un *risque relatif*, un *odds ratio*, un *hazard ratio*,..

Facteurs pronostiques de la MRC

- Pour un sujet donné, plusieurs facteurs peuvent contribuer à augmenter le risque d'évolution de la MRC vers une complication par ex. EER, maladie CV ou décès.
- Si une relation existe entre un facteur pronostique et le critère de jugement retenu (EER, maladie CV ou décès), alors on peut explorer son **intensité** comme une fonction de la *dose* et de la *durée* de l'exposition.
- Une mesure matérialise le degré de la relation entre FProno et MRC : un *excès de risque*, un *risque relatif*, un *odds ratio*,
- Et surtout un critère prenant en compte le temps, données de survie, données censures: un *hazard ratio*

Modèles pronostiques

- Les modèles pronostiques sont susceptibles de fournir pour un patient des estimations fiables des risques (ou la probabilité) de présenter un état donné ou de développer un tel état dans le futur.
- Les modèles pronostiques ont amélioré les estimations faites individuellement par les médecins.

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FRAMINGHAM HEART STUDY

A Project of the National Heart, Lung and Blood Institute and Boston University

About FHS | Participants | FHS Investigators | Risk Score Profiles | FHS Bibliography | For Researchers

- Atrial Fibrillation (10-year risk)
- Cardiovascular Disease (30-year risk)
- Congestive Heart Failure
- Coronary Heart Disease (10-year risk)
- Coronary Heart Disease (2-year risk)
- Diabetes Risk Score
- General Cardiovascular Disease (10-year risk)

Risk Score Profiles

Risk prediction estimates for the risk of various cardiovascular disease outcomes in different time horizons are available as score sheets and direct risk functions. The choice of the appropriate risk prediction algorithm should take into account the following components: cardiovascular outcome, population of interest, time horizon and risk factors. Outcome specific algorithms preceded by the descriptions of the above four components are available for the following:

Atrial Fibrillation (AF) (10-year risk) and calculator
Cardiovascular Disease (30-year risk) and calculator
Congestive Heart Failure
Coronary Heart Disease (10-year risk)
Coronary Heart Disease (2-year risk)
Diabetes Risk Score and calculator
General Cardiovascular Disease and calculator
Hard Coronary Heart Disease and calculator (10-year risk)
Hypertension Risk Score and calculator
Intermittent Claudication
Recurring Coronary Heart Disease
Stroke
Stroke after Atrial Fibrillation and calculator
Stroke or Death after Atrial Fibrillation and calculator

FRAMINGHAM HEART STUDY

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- Atrial Fibrillation (10-year risk)
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- Congestive Heart Failure
- Coronary Heart Disease (10-year risk)
- Coronary Heart Disease (2-year risk)
- Diabetes Risk Score
- General Cardiovascular Disease (10-year risk)

Men: 2-year Risk

Women: 2-year Risk

Weibull Regression Coefficients

Coronary Heart Disease (2-year risk)

(based on D'Agostino, Russell MW, Huse DM et al. 'Primary and subsequent coronary risk appraisal: new results from the Framingham Study', American Heart Journal 2000)

Outcome

First Coronary Heart Disease

Duration of follow-up

Maximum of 4 years, 2-year risk prediction score sheets

Population of interest

Individuals free of all of the following CVDs before examination:

- CHD (includes myocardial infarction, coronary insufficiency, and angina pectoris)
- stroke (ischemic or hemorrhagic)
- transient ischemic attack
- congestive heart failure
- intermittent claudication

Predictors

- Age
- Systolic blood pressure (SBP)
- Cigarette smoking status (1 if current smoker, 0 otherwise)
- Fasting lipid level (totals and HDL Cholesterol)
- Physician diagnosis of diabetes at the current or a previous examination
- Use of antihypertensive medication (yes/no)

Score de Framingham

Framingham Cardiac Risk Score

Sex (validated only for male/female, no transgender/intersex)	Female
Age (not validated for <35 or >74)	55-59
Total Chol (mg/dL)	200-239
HDL (mg/dL)	<35
BP (mm Hg) to choose a category, use the highest category.	SBP 140-149 OR DBP 90-99
Pt a diabetic?	☑ **Yes**
Pt a smoker?	☐ **Yes**
10 Year CHD Risk:	>27 %
Comparative Risk to Same Age/Sex	12 %

Score sheets for men and women from Circulation article, **Wilson, PW, et. al. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation 1998 97 (18): 1837-1847.**

Equator network

Search for reporting guidelines

Use your browser's Back button to return to your search results

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies

Reporting guideline provided for? (i.e. exactly what the authors state in the paper)

Observational studies in epidemiology (cohort, case-control studies, cross-sectional studies)

STROBE checklist: combined Word / PDF

STROBE checklist: cohort studies Word / PDF

STROBE checklist: case-control studies Word / PDF

STROBE checklist: cross-sectional studies Word / PDF

Full bibliographic reference

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

This guideline was published simultaneously in 8 journals. You can read the guideline in any of these journals using the links below.

Ann Intern Med. 2007; 147(8):573-577. PMID: 17938396
PLoS Med. 2007;4(10):e296. PMID: 17941714
BMJ. 2007;335(7624):806-808. PMID: 17947786
Prev Med. 2007;45(4):247-251. PMID: 17950122
Epidemiology. 2007;18(6):800-804. PMID: 18049194
Lancet. 2007;370(9596):1453-1457. PMID: 18064739

Explanation and elaboration papers

Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration.

The explanation and elaboration paper for this guideline was published simultaneously in 3 journals. You can read the explanation and elaboration paper in any of these journals using the links below.

PLoS Med. 2007;4(10):e297. PMID: 17941715
Epidemiology. 2007;18(6):805-35. PMID: 18049195
Ann Intern Med. 2007;147(8):W163-94. PMID: 17938389

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions
Observational studies	STROBE	Extensions
Systematic reviews	PRISMA	Extensions
Study protocols	SPIRIT	PRISMA-P
Diagnostic/prognostic studies	STARD	TRIPOD
Case reports	CARE	Extensions
Clinical practice guidelines	AGREE	RIGHT
Qualitative research	SRQR	COREQ
Animal pre-clinical studies	ARRIVE	
Quality improvement studies	SQUIRE	
Economic evaluations	CHEERS	

Translations

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EQUATOR resources in Spanish
EQUATOR resources in Portuguese

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TRIPOD statement

Search for reporting guidelines

Use your browser's Back button to return to your search results

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement

Reporting guideline provided for? (i.e. exactly what the authors state in the paper)

Reporting of studies developing, validating, or updating a prediction model, whether for diagnostic or prognostic purposes.

TRIPOD Checklist for Prediction Model Development: Word | PDF

TRIPOD Checklist for Prediction Model Validation: Word | PDF

TRIPOD Checklist for Prediction Model Development and Validation: Word | PDF

Full bibliographic reference

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions
Observational studies	STROBE	Extensions
Systematic reviews	PRISMA	Extensions
Study protocols	SPIRIT	PRISMA-P
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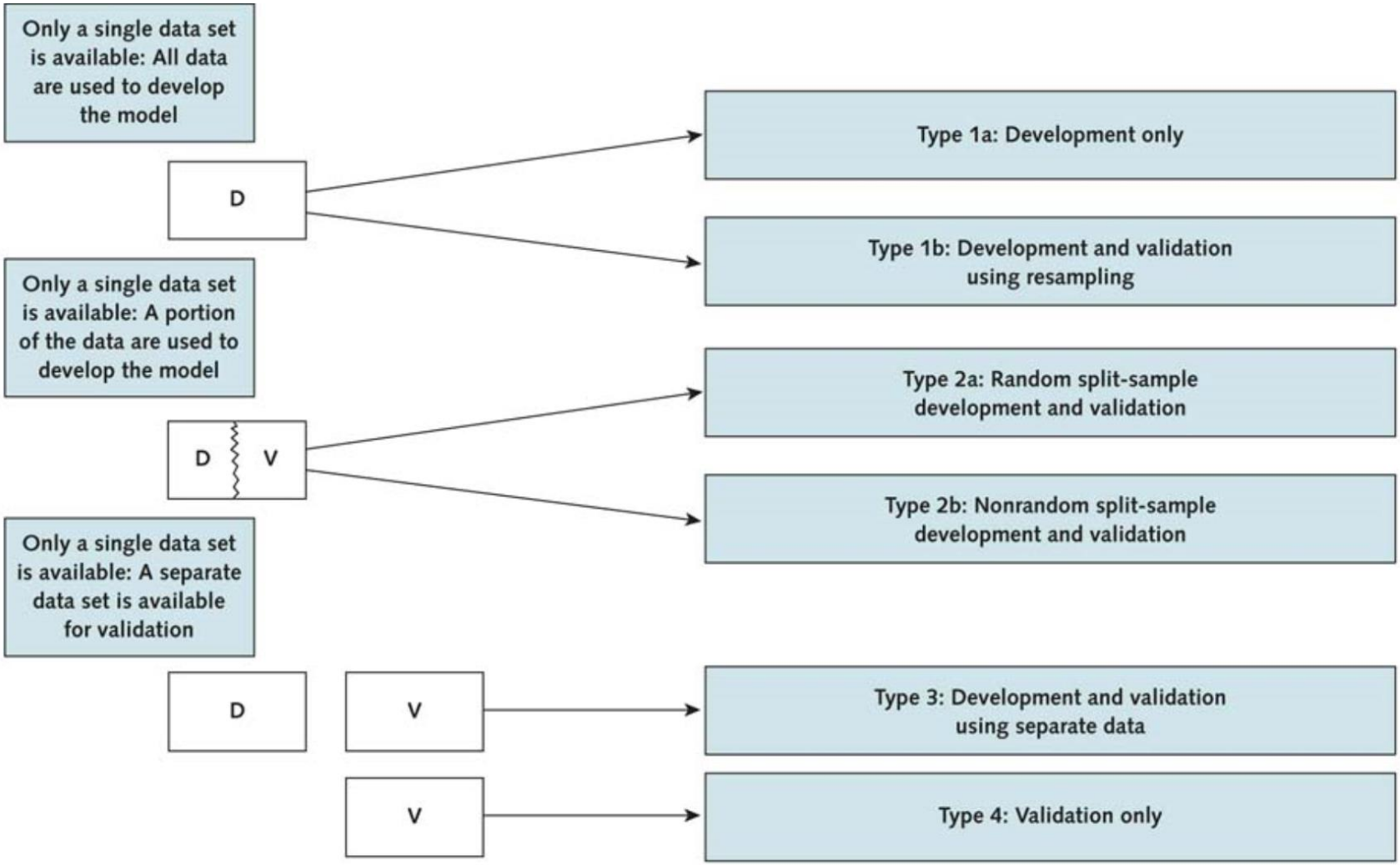
Animal pre-clinical studies	ARRIVE	
Quality improvement studies	SQUIRE	
Economic evaluations	CHEERS	

Translations

Some reporting guidelines are also available in

TRIPOD : Explanation and Elaboration



Types of prediction model studies covered by the TRIPOD statement.

D = development data; V = validation data.

Ann Intern Med. 2015;162(1):W1-W73.

Checklist TRIPOD

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	..	Specify the key study dates, including start of accrual; end of accrual; and, if	

Définition et classification de la MRC

Anomalies de la structure ou de la fonction rénale,
présente depuis plus 3 mois
avec des implications pour la santé

Criteria for CKD (either of the following present for >3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

Stadification de la MRC

Stadification de la MRC

Fondé sur la cause, le DFG et l'albuminurie

Assigner la cause de la MRC sur la présence ou l'absence de maladie systémique et le type d'atteinte parenchymateuse observée en histologie (ou présumée)

Les catégories de DFG :

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Place de l'albuminurie

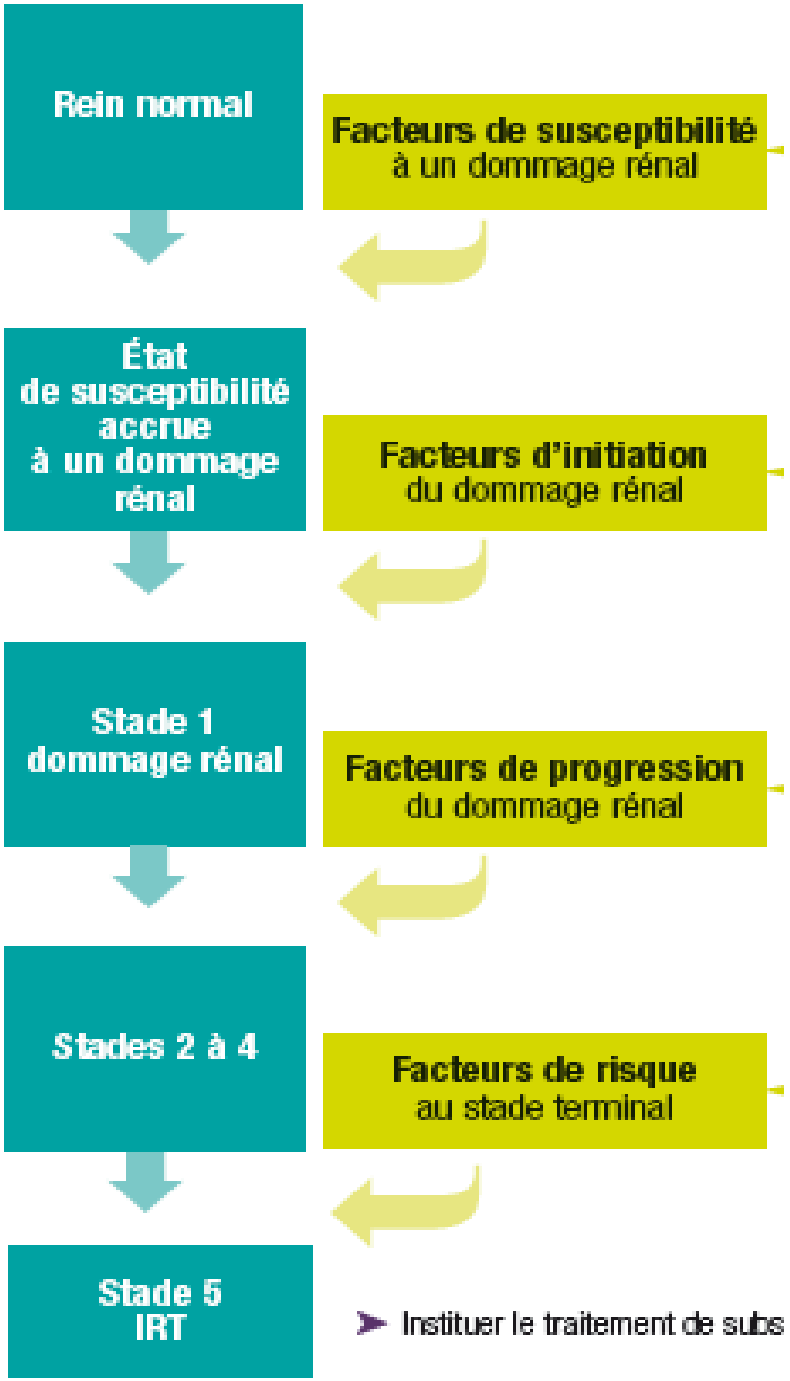
Catégories d'albuminurie

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

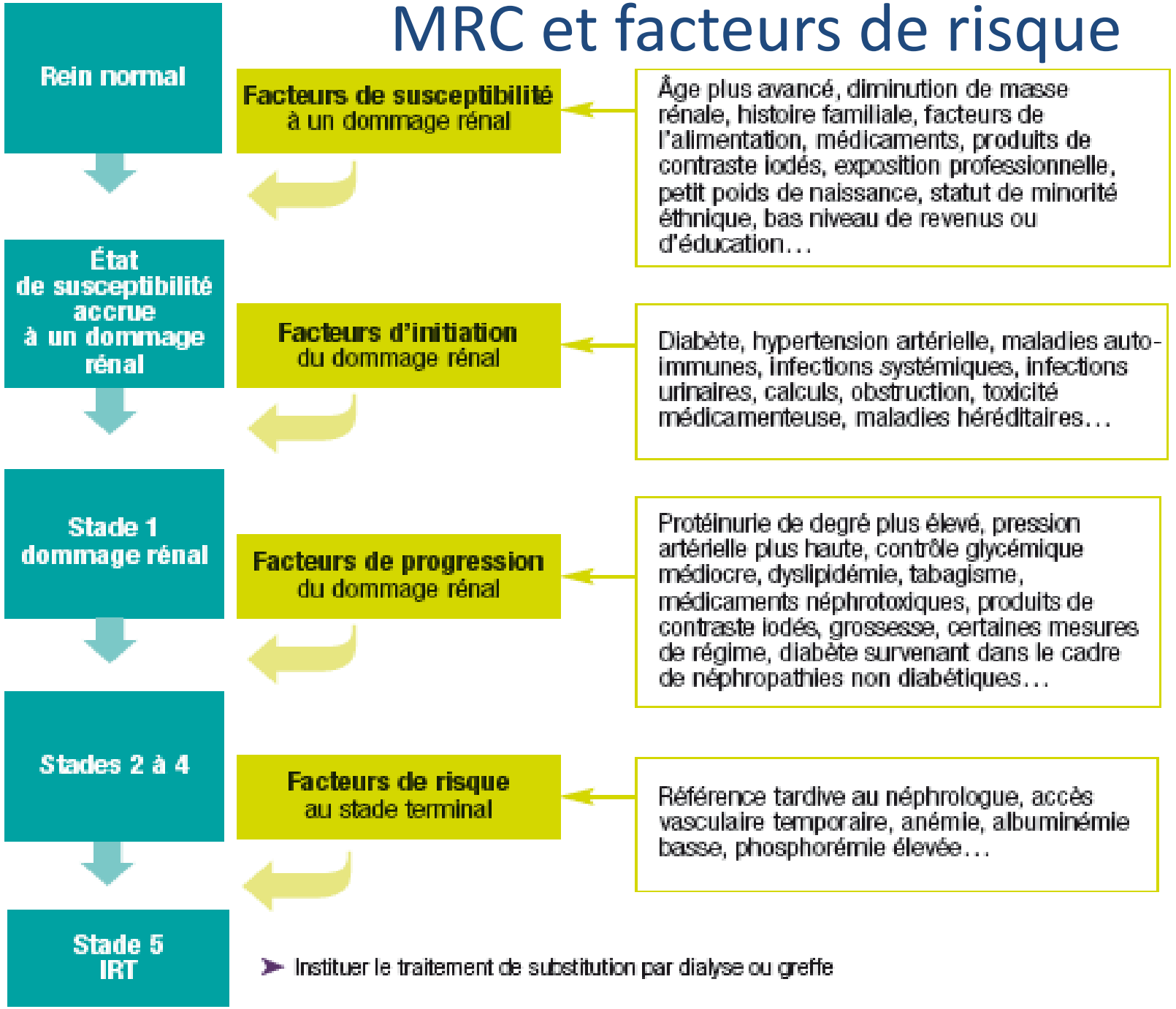
Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

*note that where albuminuria measurement is not available, urine reagent strip results can be substituted (Table 7)

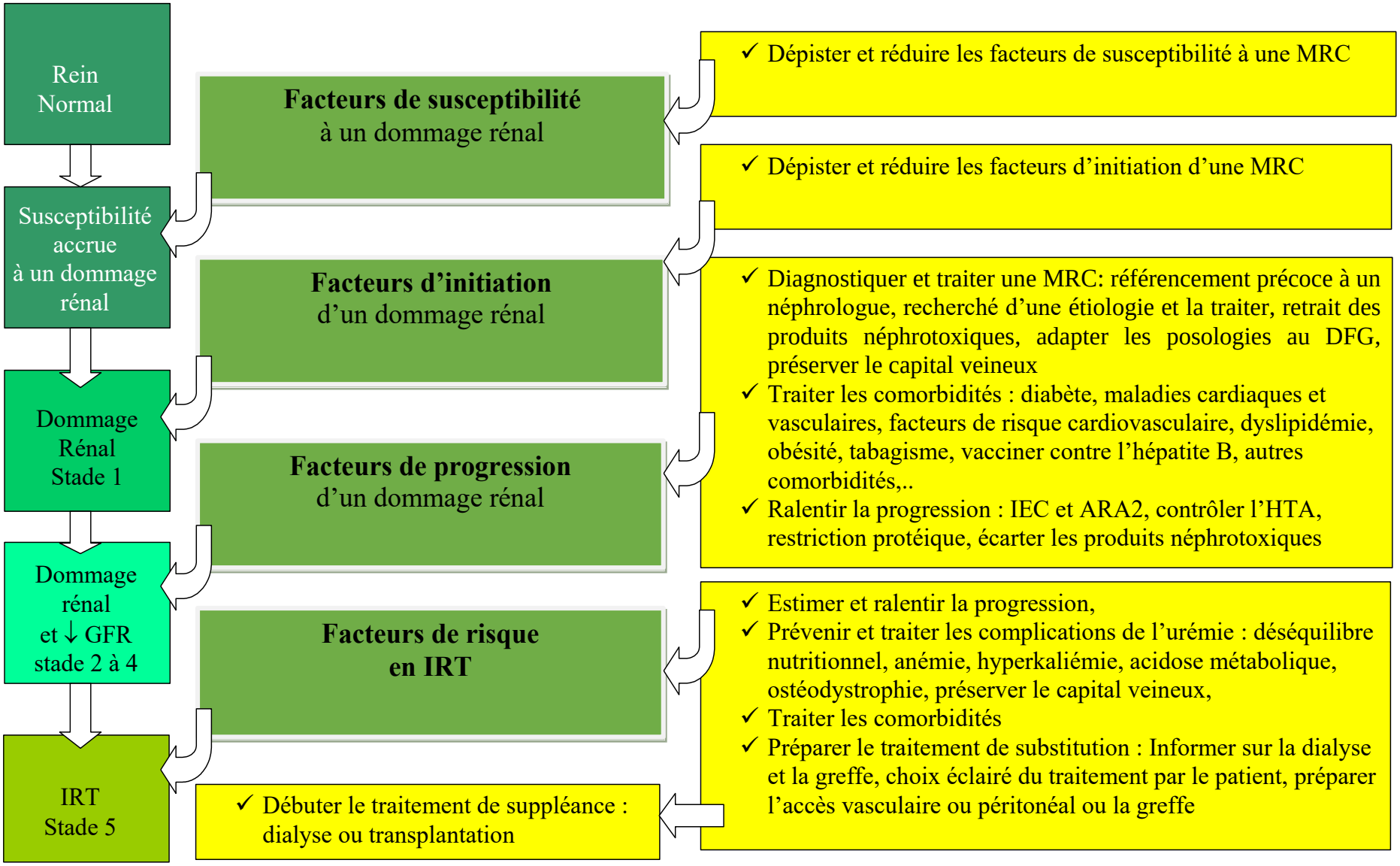


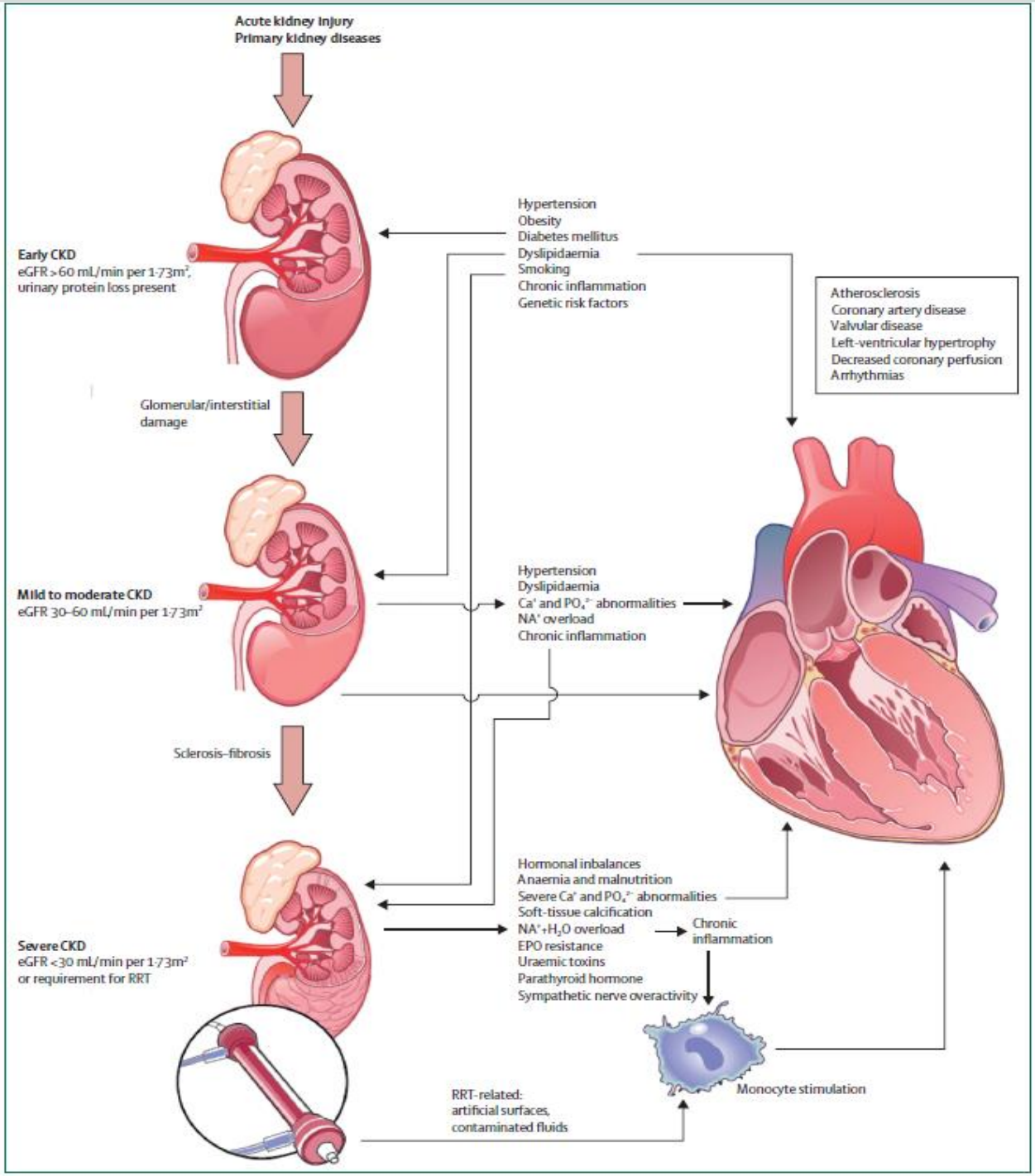
Stade de MRC et facteurs de risque

MRC et facteurs de risque



Actions à entreprendre





Physio-pathologie rein-cœur et vaisseaux

Eléments du pronostic de la MRC

Pour prédire le risque du devenir d'une MRC, identifier :

- La cause de la MRC
- Le stade de l'eDFG
- La catégorie de l 'albuminurie
- Les autres facteurs de risque
  et les comorbidités associées

Pronostic de la MRC selon le DFG et l'albuminurie

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Ref KDGIGO 2012

Evaluation de la chronicité, de la cause et du DFG

1.4.1: Evaluation of chronicity

1.4.1.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (*Not Graded*)

- If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.

1.4.2: Evaluation of cause

1.4.2.1: Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease. (*Not Graded*)

1.4.3: Evaluation of GFR

1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (*1A*)

1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (*2B*)

1.4.3.3: We recommend that clinicians (*1B*):

- use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.
- understand clinical settings in which $eGFR_{creat}$ is less accurate.

Evaluation de la MRC

We recommend that clinical laboratories should (*1B*):

- measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.
- report $eGFR_{creat}$ in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting $eGFR_{creat}$.

- report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.

When reporting serum creatinine:

- We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (µmol/l) and rounded to the nearest 100^{th} of a whole number when expressed as conventional units (mg/dl).

Estimation du DFG : CKD-EPI

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \_ 1.159 \text{ [if black]}$$

where Scr is serum creatinine,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr/κ or 1,

max indicates the maximum of Scr/κ or 1.

Lewey et al. Annals of Internal Medicine 2009;150(9):604-613

Estimation du DFG : CKD-EPI

	Development (n=5,504)	Internal validation (n=2,750)	External validation (n=3,896)	P values *
Mean age (SD), *y*	47 (15)	47 (15)	50 (15)	p<0.001
Age, *n (%)*				p<0.001
<40 y	2058 (37)	1018 (37)	1136 (29)	
41-65 y	2751 (50)	1403 (51)	2192 (56)	
>65 y	695 (13)	329 (12)	568 (15)	
66-70 y	476 (9)	220 (8)	254 (7)	
71-75 y	150 (3)	66 (2)	185 (5)	
76-80 y	41 (0)	30 (1)	92 (2)	
>80 y	28 (0)	13 (0)	37 (0)	
Women, *n (%)*	2391 (43)	1215 (44)	1767 (45)	p=0.084
Race, *n (%)*				p<0.001
Black	1728 (32)	857 (31)	384 (10)	
Hispanic	247 (5)	106 (4)	67 (2)	
Asian	62 (1)	38 (1)	67 (2)	
White and other	3467 (63)	1749 (64)	3378 (87)	
Kidney donor, *n (%)*	694 (13)	336 (12)	608 (16)	p<0.001
Transplant recipient, *n (%)*	241 (4)	119 (4)	1134 (29)	p<0.001
Diabetes, *n (%)*	1581 (29)	825 (30)	1089 (28)	p=0.173
Mean height (SD), *cm*	170 (10)	170 (10)	170 (10) †	p=0.90
Mean weight (SD), *kg*	82(20)	82 (20)	79 (18)	p<0.001
Mean body mass index (SD), *kg/m2*	28 (6)	28 (6)	27 (6) †	p<0.001
Mean body surface area (SD), *m2*	1.93 (0.20)	1.93 (0.20)	1.90 (0.23) †	p<0.001
Mean GFR (SD), *mL/min per 1.73 m2* ‡	68 (40)	67 (40)	68 (36)	p=0.70
Mean serum creatinine level (SD)				p<0.001
µmol/L	146 (106)	148 (106)	134 (88)	
mg/dL	1.65 (1.20)	1.67 (1.20)	1.52 (1.00)	

GFR = glomerular filtration rate.

* For comparison of the combined development and internal validation data sets vs. the external validation data set.

† The sample size is 3875 because of missing data.

Evaluation de la MRC

We suggest measuring cystatin C in adults with $eGFR_{creat}$ 45–59 ml/min/1.73 m^2 who do not have markers of kidney damage if confirmation of CKD is required. (*2C*)

- If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is also <60 ml/min/1.73 m^2, the diagnosis of CKD is confirmed.
- If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is ≥ 60 ml/min/1.73 m^2, the diagnosis of CKD is not confirmed.

If cystatin C is measured, we suggest that health professionals (*2C*):

- use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.
- understand clinical settings in which $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ are less accurate.

Albuminurie

We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) (*2B*):

1) urine albumin-to-creatinine ratio (ACR);
2) urine protein-to-creatinine ratio (PCR);
3) reagent strip urinalysis for total protein with automated reading;
4) reagent strip urinalysis for total protein with manual reading.

We recommend that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone. (*1B*)

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (*Not Graded*)

Albuminurie

Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (*Not Graded*):

- Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.
- Confirm ACR $\geq$ 30 mg/g ($\geq$ 3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample.
- If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.

If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., α_1-microglobulin, monoclonal heavy or light chains, [known in some countries as "Bence Jones" proteins]). (*Not Graded*)

Progression de la MRC

Definition and identification of CKD progression

Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/or where measurement will impact therapeutic decisions (see figure below). (*Not Graded*)

Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. (*Not Graded*)

Define CKD progression based on one of more of the following (*Not Graded*):

- Decline in GFR category ($\geq$90 [G1], 60–89 [G2], 45–59 [G3a], 30–44 [G3b], 15–29 [G4], $<$15 [G5] ml/min/1.73 m^2). A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.
- Rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/yr.
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.

In people with CKD progression, as defined in Recommendation 2.1.3, review current management, examine for reversible causes of progression, and consider referral to a specialist. (*Not Graded*)

Fréquence de surveillance

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

Importance de la protéinurie

- La définition de la maladie rénale chronique ne tient pas compte, dans les stades 3 à 5, de la présence ou non d'une protéinurie
- or, la protéinurie est le plus fort prédicteur du risque de progression vers l'insuffisance rénale terminale et un puissant prédicteur du risque d'atteinte cardiovasculaire.

Gansevoort RT, de Jong PE. Curr Opin Nephrol Hypertens 2010;19:308.

http://www.soc-nephrologie.org/esociete/groupes/proteinurie/index.htm

Maladie rénale chronique

- Sur deux périodes,1988-1994 et 1999-2004, la prévalence de la MRC a augmenté : de 10,0 % à 13,1 %.
- Le stade 3 a augmenté de façon constante : de 5,4 % à 7,7 %.
- Europe, étude Hunt II : prévalence de MRC proche de celle des États-Unis. Cependant, à 60 ans, le rapport IRT/IRC était 2 fois plus élevé aux États-Unis qu'en Norvège et 3 fois *après* 60 ans.
- Étant donné que la prévalence de la MRC est similaire, ainsi la progression vers l'insuffisance rénale terminale apparaît plus importante aux États-Unis qu'en Norvège.

USRDS 2006 Annual Data Report ; Coresh J et al. *JAMA* 2007 ;298(17) :2038-47
Hallan SI et al. *JASN* 2006 ;17(8) :2275-84.

Prévalence MRC selon le stade

- Global mean CKD prevalence : 13.4%(11.7–15.1%),
- Stages 3–5 was 10.6%(9.2–12.2%).

- CKD prevalence by stage:
  - Stage-1: eGFR>90+ACR>30, 3.5% (2.8–4.2%);
  - Stage-2: eGFR 60–89+ACR>30, 3.9% (2.7–5.3%);
  - Stage-3: eGFR 30–59, 7.6% (6.4–8.9%);
  - Stage-4: eGFR 29–15, 0.4% (0.3–0.5%);
  - Stage-5: eGFR<15, 0.1% (0.1–0.1%).

Prévalence de la MRC par grandes régions géographiques

Table 1. Mean prevalence of CKD split by geographical region with 95% Confidence Intervals.

	Stage 1 to 5		Stages 3 to 5	
	N*	Prevalence (%)	N*	Prevalence (%)
S Africa, Senegal, Congo	5,497	8.66 (1.31, 16.01)	1,202	7.60 (6.10, 9.10)
India, Bangladesh	1,000	13.10 (11.01, 15.19)	12,752	6.76 (3.68, 9.85)
Iran	17,911	17.95 (7.37, 28.53)	20,867	11.68 (4.51, 18.84)
Chile	0	NONE	27,894	12.10 (11.72, 12.48)
China, Taiwan, Mongolia	570,187	13.18 (12.07, 14.30)	62,062	10.06 (6.63, 13.49)
Japan, S Korea, Oceania	654,832	13.74 (10.75, 16.72)	298,000	11.73 (5.36, 18.10)
Australia	12,107	14.71 (11.71, 17.71)	896,941	8.14 (4.48, 11.79)
USA, Canada	20,352	15.45 (11.71, 19.20)	1,319,003	14.44 (8.52, 20.36)
Europe	821,902	18.38 (11.57, 25.20)	2,169,183	11.86 (9.93, 13.79)

*N is number of participants in the sample estimate.

Hill NR et al. PLoS ONE 2016; 11 (7): e0158765. doi:10.1371/journal.pone.0158765

La MRC : un enjeu de santé publique

- 1 personne sur 10 MRC ;
- 4 personnes sur 100.000 atteindront l'IRT.
- Chez les patients < âgé de 80 ans, le risque annuel d'IRT dans les 5 ans est de 42 pour 10^5.
-
- L'IRT reste rare: 0.1 % de la population française
- Toutefois, le coût de la dialyse est élevé, plus de 2 % des dépenses de santé.

Risch L, et al : Clin Chim Acta 2007 ;378(1-2) :71-7.

Benain JP, et al : Néphrol Thérap 2007 ;3 : 96–106.

Épidémiologie et référencement tardif

- Le référencement tardif (RT) au néphrologue existe toujours
- Etre âgé, appartenir à une minorité, être moins instruit, sans assurance sociale, souffrir de multiples comorbidités et le manque de communication entre médecins de ville et néphrologues contribuent au RT.
- Une prise en charge néphrologique en pré-dialyse plus longue contribue à la réduction des taux d'hospitalisation et de la mortalité
- Le RT est une source de coûts évitables. En France, les économies potentielles ont été estimées à 30 millions d'euros par an.

Chan MR, et al *Am J Med* 2007, **120:**1063-70. Stack AG. *Am J Kidney Dis* 2003, **41:**310-318. Jungers P, Joly D et al : Presse Med 2006 ;**35** :17-22.

Qui adresser au néphrologue (1) ?

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Qui adresser au néphrologue (2) ?

- diminution rapide de l'eGFR :
  > 5 ml/min/1.73 m2 en 1 an,
  ou >10 ml/min /1.73 m2 en 5 ans

- hypertension mal contrôlée malgré une quadrithérapie à doses thérapeutiques

- patient présentant, ou suspect d'avoir, une cause rare ou génétique de MRC

- suspicion de sténose artérielle rénale.

A qui faire une recherche de MRC?

- Diabète
- HTA
- Maladie cardiovasculaire : cardiopathie ischémique, insuffisance cardiaque chronique, maladie vasculaire périphérique et maladie cérébrovasculaire
- Anomalie morphologique rénale, lithiase rénale ou hypertrophie prostatique
- Affection multisystémique avec atteinte rénale potentielle (ex: LEAD)
- Histoire familiale de MRC stade 5, ou de maladie rénale héréditaire
- Découverte fortuite d'une hématurie ou d'une protéinurie.

IRT, dialyse et greffe

- Chaque année, environ 11.000 personnes débutent un traitement de suppléance.
- 84.683 patients traitées en France en 2016
- dont 55 % par dialyse et 45 % par greffe rénale.
- En augmentation chaque année avec le vieillissement de la population, notamment dans la classe d'âge des 75-84 ans qui a l'incidence la plus élevée.
- L'hypertension et le diabète sont présents à eux seuls dans près d'un cas sur deux.

MRC et risque cardiovasculaire

- In patients with CKD (compared with the general population), cardiovascular disease is **more frequent and severe**, often **not recognized**, and **undertreated**
- Patients with CKD should be viewed among the **highest-risk groups for cardiovascular events and disease**, and require special clinical attention at an individual patient level, in the development of guidelines, and in the defining of research priorities
- The strong causal association between CKD and cardiovascular risk implies that to **prevent progression of CKD** is, by definition, to prevent cardiovascular disease

Gansevoort RT et al. Lancet 2013; 382: 339–52

MRC et risque cardiovasculaire

- In patients with CKD, the increased cardiovascular risk is **multifactorial** and is due partly to pathophysiological processes **specific to CKD** that make prevention of cardiovascular disease by standard interventions directed at single traditional risk factors difficult; therefore, innovative strategies need to be investigated (eg, the targeting of non-traditional cardiovascular risk factors, early prevention, and multifactorial intervention strategies)

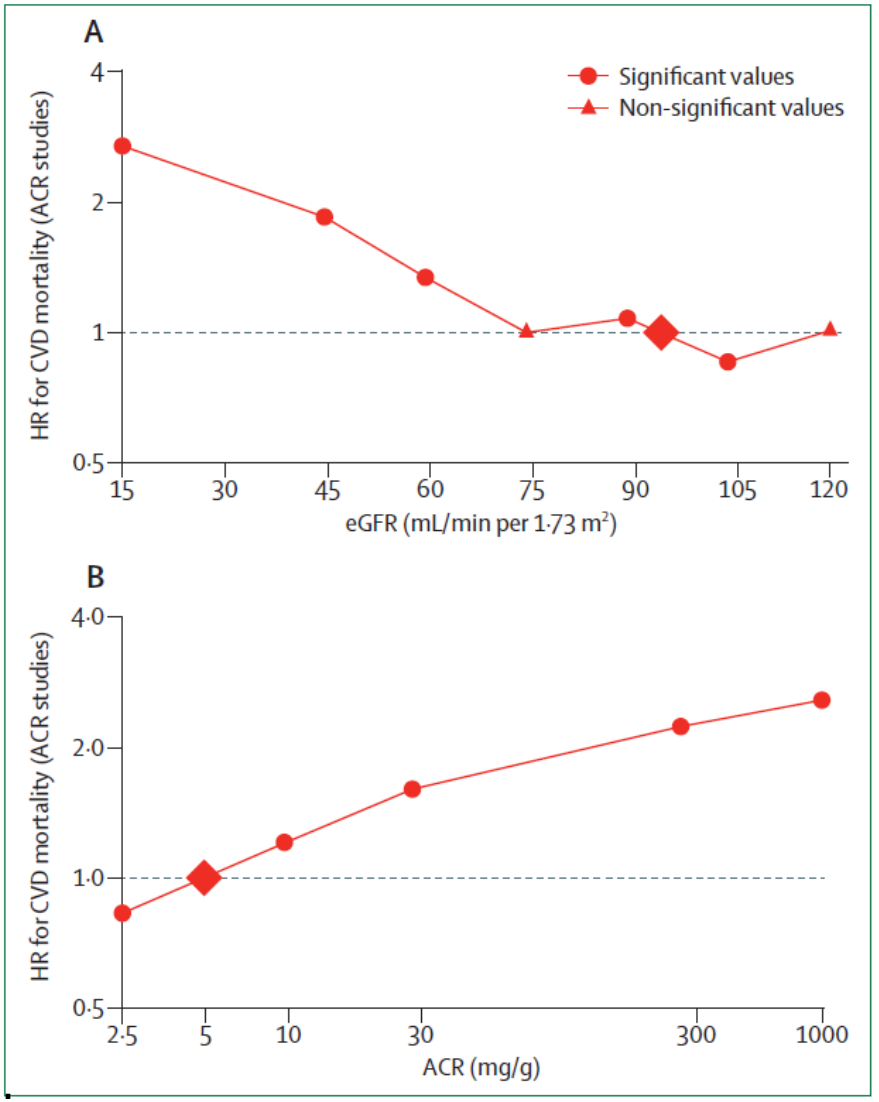
Gansevoort RT et al. Lancet 2013; 382: 339–52

Fonction rénale, protéinurie et mortalité cardiovasculaire

(A) Fonction rénale (eGFR);
ref: 95 mL/min per 1.73 m2 ◆

(A) Albuminurie (ACR) :
ref: 5 mg/g ◆

HR adjusted for eGFR or ACR, age, sex, ethnic origin, and traditional CV risk factors.
ACR=albumin-to-creatinine ratio.



Matsushita K, et al. *Lancet* 2010; **375:** 2073–81.

Fonction rénale, protéinurie et mortalité cardiovasculaire

- The adjusted risk of cardiovascular mortality is **more than doubled** *at the upper end of the microalbuminuria category* (30–299 mg/g), compared with the risk in individuals with normal albuminuria.
- **Albuminuria** *even at the upper end of the normal range* (threshold 30 mg/g) confers **CV risk**.
- Thus, even **slight increases** in albuminuria require clinical attention.
- A wide variety of specific CVD have been associated with estimated impaired kidney function.

Fonction rénale, protéinurie et mortalité cardiovasculaire

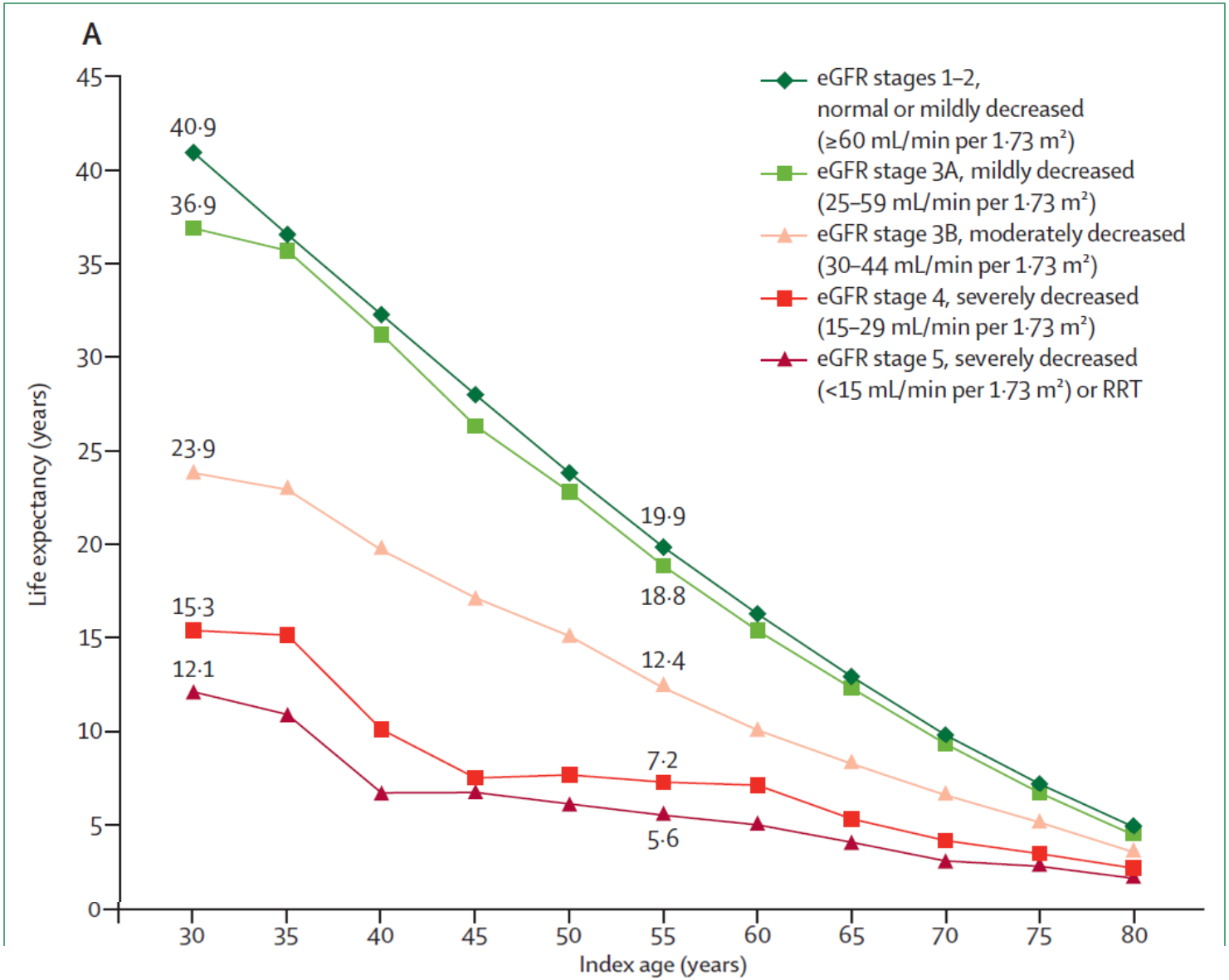
- Risk of heart failure is ~ doubled in patients with estimated GFR < 60 mL/min per 1.73 m^2 compared that in people with preserved estimated GFR. The risk is similarly increased for stroke, peripheral artery disease, coronary heart disease, and atrial fibrillation.
- The associations between CKD and CVD are largely irrespective of age, sex, and ethnic origin, from US, European,Taiwanese, and South Korean general-population cohorts.

Fonction rénale, protéinurie et mortalité cardiovasculaire

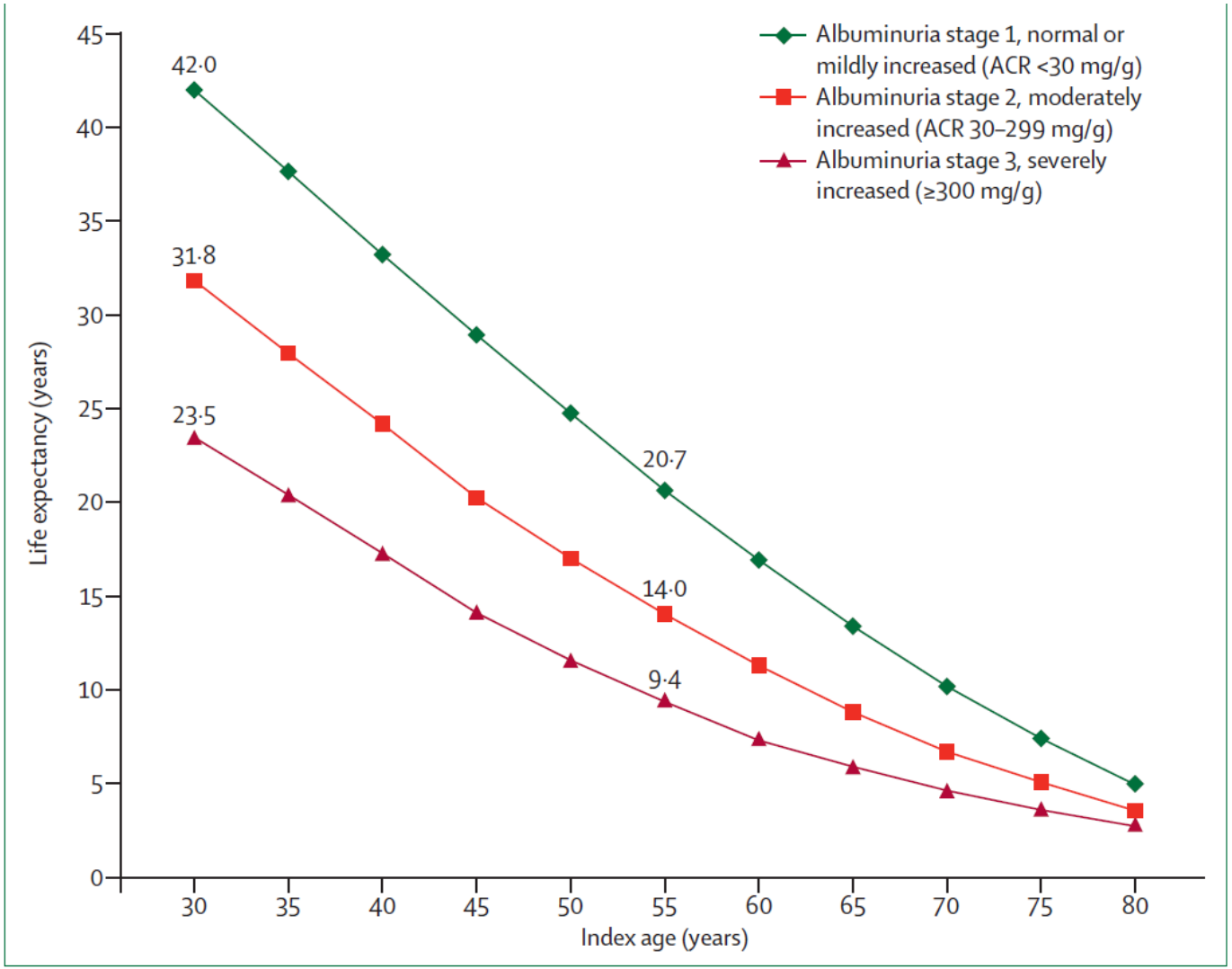
- CKD is frequently the result of hypertension and diabetes mellitus.
- Meta-analyses showed, however, that impaired kidney function and raised albuminuria are CV risk factors **independently** of *hypertension* and *diabetes mellitus*.
- 40–50% of patients with low eGFR and high albuminuria do **not** have diabetes or hypertension.
- in these patients, eGFR and albuminuria associated with CV mortality are similar to those in individuals with CKD who **do have** diabetes or hypertension.

Fox CS et al. *Lancet* 2012; 380: 1662–73. Mahmoodi BK et al. *Lancet 2012;* 380: 1649–61.

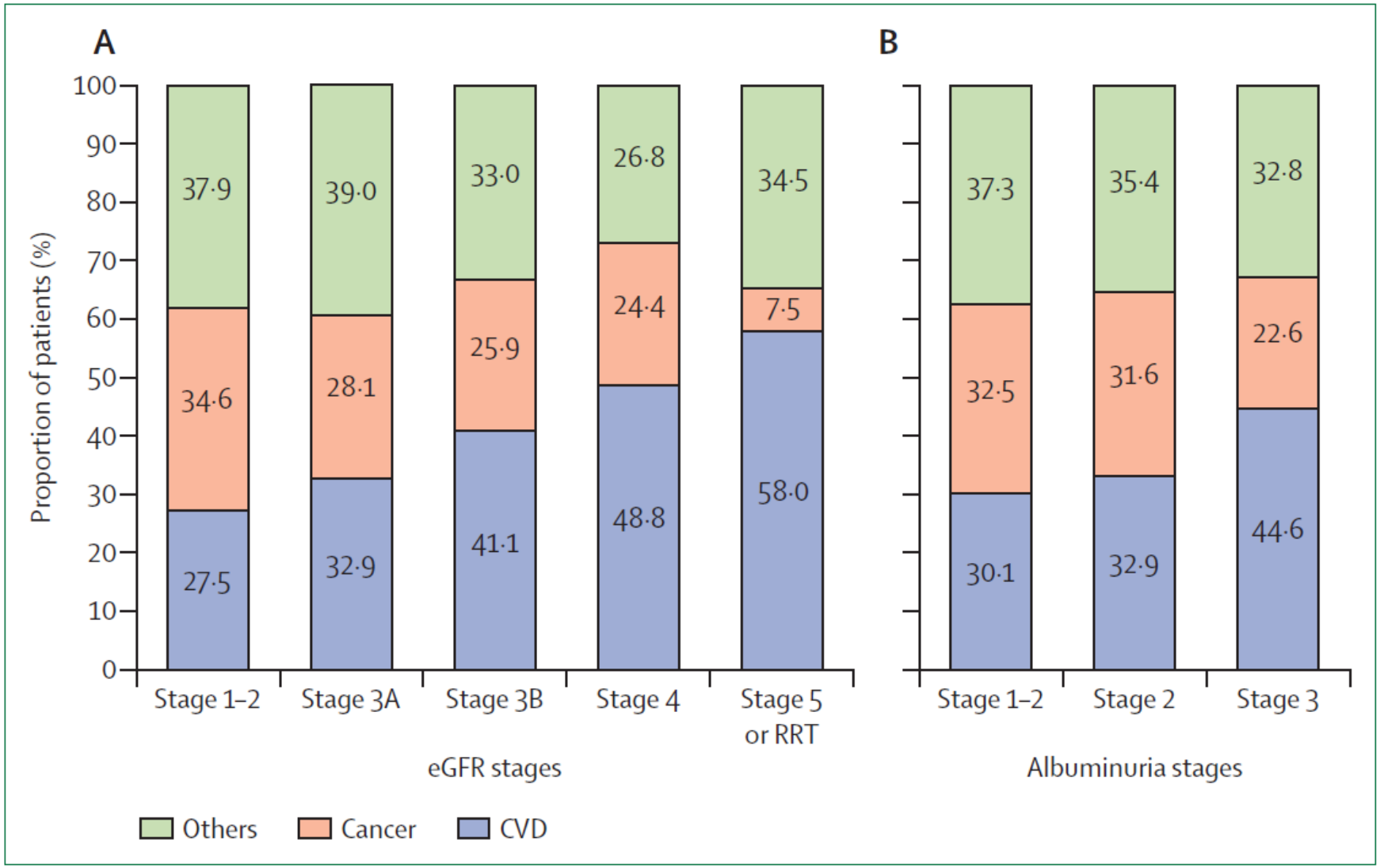
Stade de MRC et eGFR



Stade de MRC et albuminurie



Stade de la MRC et décès CV



Turin TC et al. *Nephrol Dial Transplant* 2012; **27:** 3182–86. Turin TC et al. *Am J Kidney Dis* 2013; **61:** 646–68.

De nombreuses études sur le risque vasculaire et sa prévention

- **ALLHAT** (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial),
- **SEARCH** (Study Evaluating Additional Reductions in Cholesterol and Homocysteine),
- **TNT** (Treating to New Targets),
- **IDEAL** (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering),
- **ALLIANCE** (Aggressive Lipid Lowering Initiation Abates New Cardiac Events),
- **PROVE IT** (Pravastatin or Atorvastatin in Evaluation and Infection Therapy),

… depuis une décade (2)

- **PROSPER** (Prospective Study of Pravastatin in the Elderly at Risk),
- **FIELD** (Fenofibrate Intervention and Event Lowering in Diabetes),
- **CARDS** (Collaborative Atorvastatin Diabetes Study),
- **ASPEN** (Atorvastatin as Prevention of Coronary Heart Disease Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus),
- **SPARCL** (Stroke Prevention by Aggressive Reduction in Cholesterol Levels),
- **ACCORD** (Action to Control Cardiovascular Risk in Diabetes).
- **ALERT** (Assessment of Lescol in Renal Transplantation),

… depuis une décade (3)

- **4D** (Die Deutsche Diabetes Dialyse Studie),
- **PREVEND IT** (Prevention of REnal and Vascular ENdstage Disease Intervention Trial),
- **AURORA** (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events),
- **SHARP** (Study of Heart and Renal Protection).

Evaluation du statut lipidique chez l'adulte avec MRC

- In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (1C)
- In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients. (Not Graded)

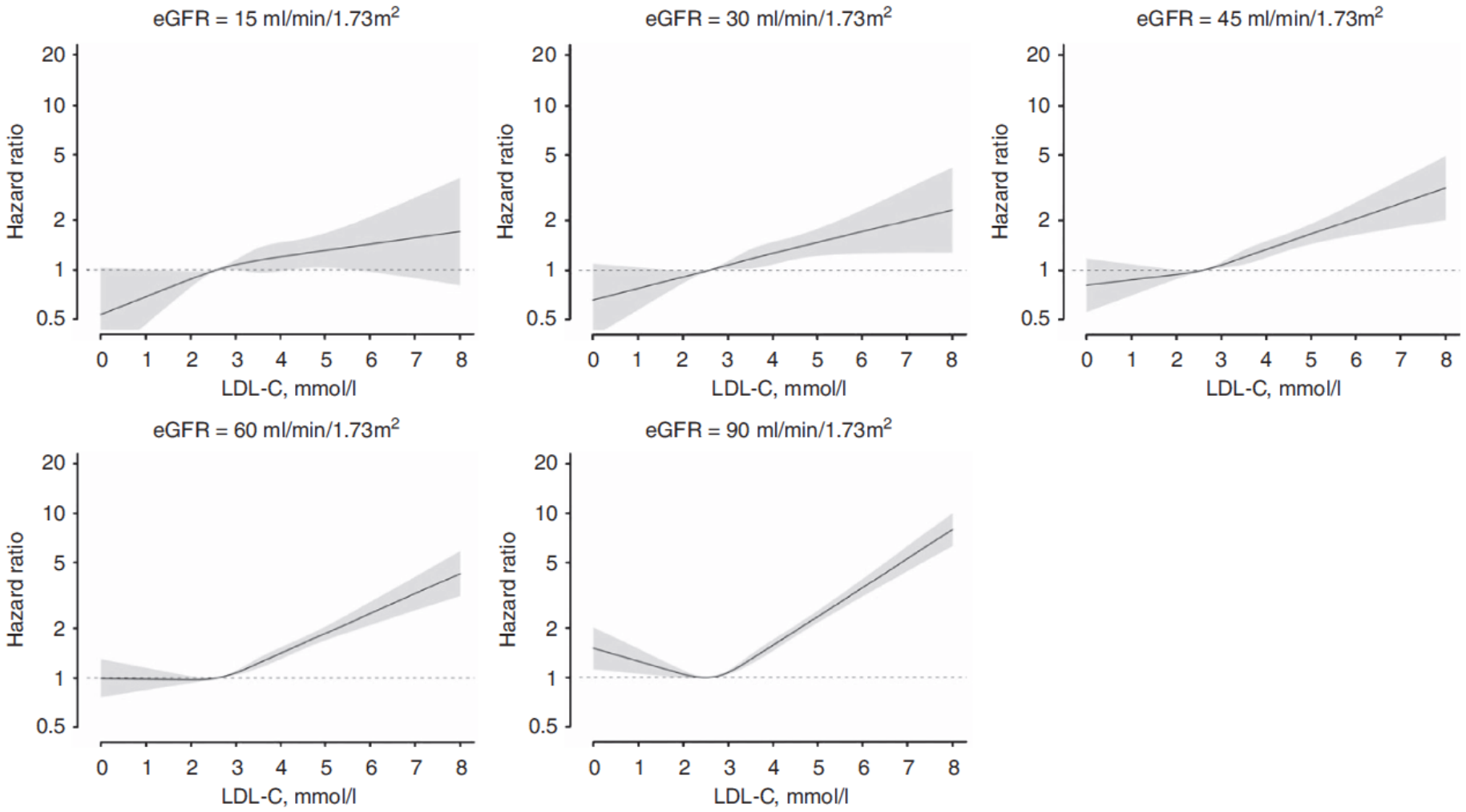
Kidney International Supplements (2013) 3, 263–265

Abaissement pharmacologique de la cholestérolémie chez l'adulte : rationnel

- Dyslipidemia is common in people with CKD but LDL-C does not reliably discriminate between those at low or high risk of cardiovascular events.

Kidney International Supplements (2013) 3, 263–265

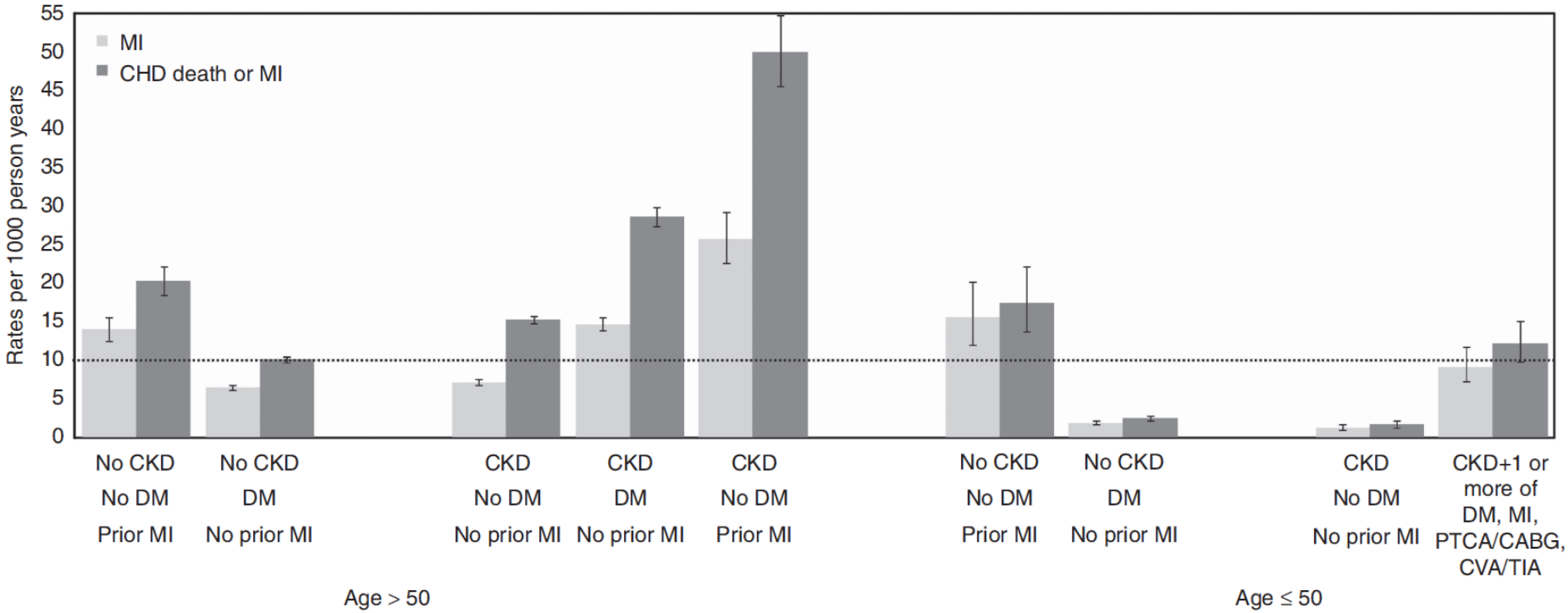
LDL-C et HRa d'infarctus du myocarde selon DFG



Suivi : 48 mois

J Am Soc Nephrol 2013; 24: 979–986

Risque à 10 ans selon l'âge, une MRC, un IdM et un diabète décès CV ou IdM



Décès d'origine coronarienne ou IdM non fatal en fonction du DFG

Table 3 | Rate of coronary death or non-fatal MI (by age and eGFR)

	Rate (95% CI) of coronary death or non-fatal MI (per 1000 patient-years)		
	Overall	Male	Female
Age >40 years (eGFR G1-G4)	14.9 (14.6–15.3)	17.4 (16.9–17.9)	12.7 (12.3–13.1)
eGFR G3a-G4	19.3 (18.8–19.8)	23.4 (22.6–24.2)	16.4 (15.8–17.0)
eGFR G1-G2	9.7 (9.3–10.0)	12.0 (11.4–12.6)	6.7 (6.3, 7.2)
Age >50 years (eGFR G1-G4)	17.3 (17.0–17.7)	20.2 (19.6–20.8)	14.8 (14.3–15.3)
eGFR G3a-G4	19.9 (19.4–20.4)	24.3 (23.4–25.2)	16.9 (16.3–17.5)
eGFR G1-G2	12.9 (12.4–13.4)	15.2 (14.5–16.0)	9.7 (9.0–10.5)
Age 40–50 years (eGFR G1-G4)	3.2 (2.9–3.6)	4.7 (4.2–5.4)	1.6 (1.2–2.0)
eGFR G3a-G4	4.7 (3.7–6.0)	5.9 (4.3–8.1)	3.6 (2.5–5.3)
eGFR G1-G2	3.0 (2.6–3.3)	4.6 (4.0–5.3)	1.2 (0.9–1.6)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.
Data are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. People with diabetes, MI, and other cardiovascular disease were included. Data do not apply to people with kidney transplants.

Abaissement pharmacologique de la cholestérolémie chez l'adulte (1)

- In adults aged ≥ 50 years with eGFR < 60 ml/min/1.73m2 but not treated with chronic dialysis or kidney transplantation, we recommend treatment with a statin or statin/ezetimibe combination. (1A)
- In adults aged ≥ 50 years with CKD and eGFR ≥ 60 ml/min/1.73 m2 we recommend treatment with a statin. (1B)

Kidney International Supplements (2013) 3, 263–265

Abaissement pharmacologique de la cholestérolémie chez l'adulte (1)

- In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with ≥ 1 of the following (2A):
  - known coronary disease (myocardial infarction or coronary revascularization);
  - diabetes mellitus;
  - prior ischemic stroke;
  - estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%.

Kidney International Supplements (2013) 3, 263–265

Abaissement pharmacologique de la cholestérolémie chez l'adulte (2)

- In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination *not* be initiated. (2A)
- In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents *be continued*. (2C)
- In adult kidney *transplant* recipients, we suggest treatment with *a statin*. (2B)

Kidney International Supplements (2013) 3, 263–265

Traitement hypotriglycéridémiant chez l'adulte

- 5.1: In adults *with CKD* (including those treated with chronic dialysis or kidney transplantation) *and* hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. (2D)

Kidney International Supplements (2013) 3, 263–265

Recommandations résumées (1)

- (a) Rule out remediable causes of secondary dyslipidemia.
- (b) Establish the indication of treatment and select agent and dose.
- (c) Treat according to a ‘‘fire-and-forget’’ strategy: do not measure LDL-C unless the results would alter management.
- When establishing the diagnosis of CKD, a full lipid profile is part of routine care. Rule out remediable causes of *secondary* dyslipidemia. If excluded, establish whether *statin* treatment is indicated based on underlying cardiovascular risk. If the level of risk suggests that statin treatment is indicated, select a dose of a statin that has been tested for safety in people with CKD.

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Recommandations résumées (2)

- Contemporary practice emphasizes the use of targets for LDL-C (e.g., 1.8 or 2.6 mmol/l), which require *repeated* measurements of LDL-C and treatment *escalation* with higher doses of statin or initiation of combination lipid-lowering therapy when the LDL-C target is not met. (‘‘treat-to-target’’ strategy)
- KDIGO does *not* recommend the treat-to target strategy : it has never been proven beneficial in any clinical trial. Higher doses of statins have not been proven to be safe in CKD.
- A ‘‘fire-and-forget’’ strategy is recommended for CKD .
- Follow-up measurement of lipid levels may be performed in patients for whom these measurements are judged to favorably influence *adherence* to treatment or other processes of care.

Aide à la décision thérapeutique

- Coronary risk is sufficiently high to justify prescription of statins in people aged ≥ *50* with *non*-dialysis-dependent *CKD* or a kidney *transplant*.
- Coronary risk in patients < *50* years with *non*-dialysis dependent CKD is *lower*, but the presence of additional CV risk factors may increase risk to justify statin prescription. Given the evidence that treatment with statins improve vascular outcomes in this population, treatment is *suggested* for in these patients with known vascular disease (prior MI, coronary revascularization or stroke), diabetes, or other risk factors that increase the 10-year risk of coronary death or non-fatal MI (risk calculator estimation) to >10%.

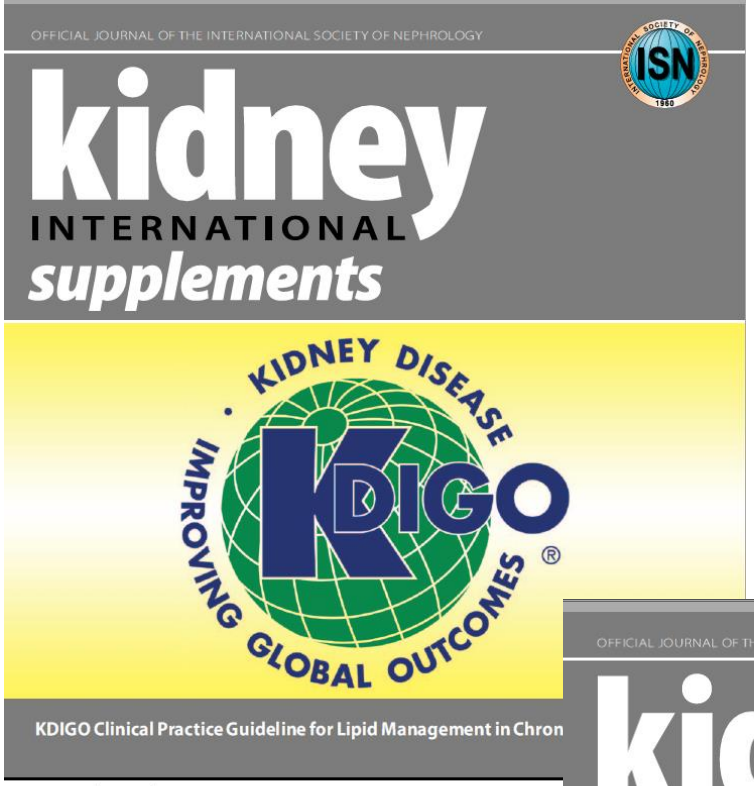
Conclusion (1)

- CKD affects as many as 10–15% of the population worldwide, and is due to multiple causes,
- Is associated with impaired quality of life and strongly reduced life expectancy,
- Is associated with increased risk of CVD, different disease manifestations, and more frequent and severe CVD outcomes,
- Reflects a serious complication of many different diseases, including diabetes, hypertension, and systemic immune disorders,
- Its cause remains uncertain in a large proportion of affected individuals, hindering specific therapeutic approaches.

Conclusion (2)

- The mechanisms that cause progressive kidney failure and associated systemic complications, including CVD, remain incompletely understood, resulting in few available targeted therapies
- CKD and AKI are related manifestations of renal impairment with mutual predisposition, functional and structural overlap, and potentiating adverse consequences
- The costs of treating CKD-associated complications (including kidney failure) provide a challenge for health-care budgets that cannot be met in many parts of the world
- Successful prevention and treatment of CKD is strongly linked to progress on the Sustainable Development Goals.

***Levin A et al. Lancet* 2017; 390: 1888–917**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VOLUME 3 | ISSUE 3 | NOVEMBER 2013
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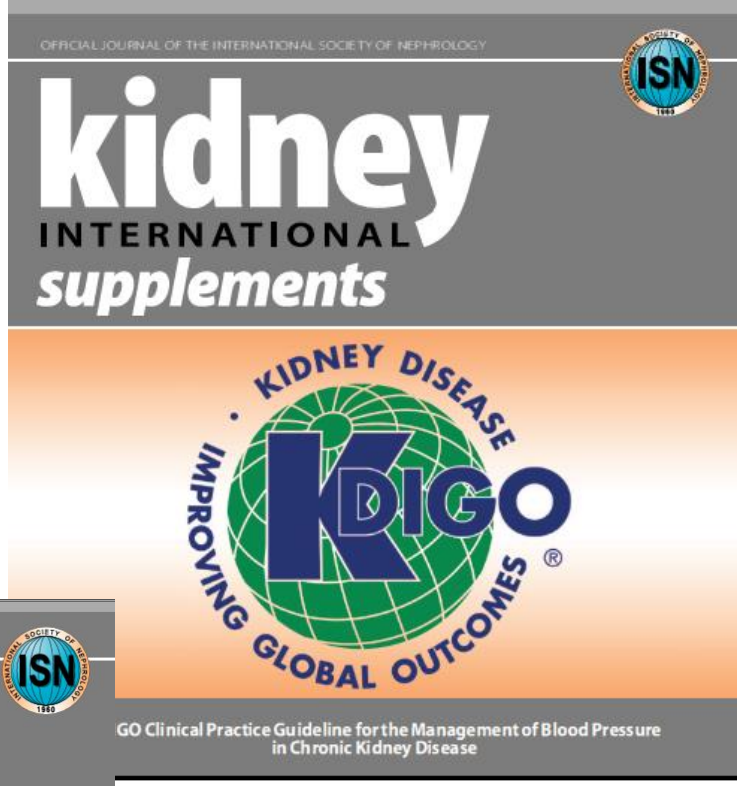
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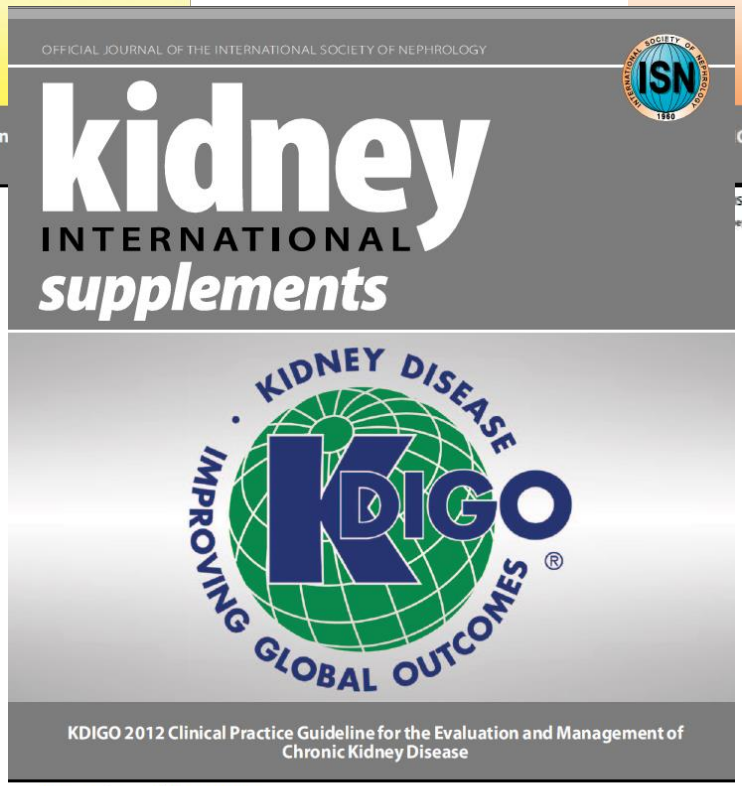
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Merci pour votre attention