Welcome to the

KDIGO Controversies Conference on Central & Peripheral Arterial Diseases in CKD

#KDIGOVASCULAR

CVD Series Overview

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DISCLOSURES

Charles A. Herzog, MD, FACC, FAHA

Disclosure of Relevant Financial Relationships

- Consultant: AbbVie, Amgen, AstraZeneca, Corvidia, Diamedica, FibroGen, Janssen, NxStage, Pfizer, Relypsa, Sanifit, University of Oxford
- Grant/Research support: Amgen, Bristol-Myers Squibb, NHLBI/NIDDK (NIH), Relypsa, University of British Columbia
- Honoraria: UpToDate
- Stockholder: Boston Scientific, Bristol-Myers Squibb, General Electric, Johnson & Johnson, Merck
- Employer: Hennepin Healthcare

Cardiovascular Disease in CKD Controversies Conferences: A Brief History

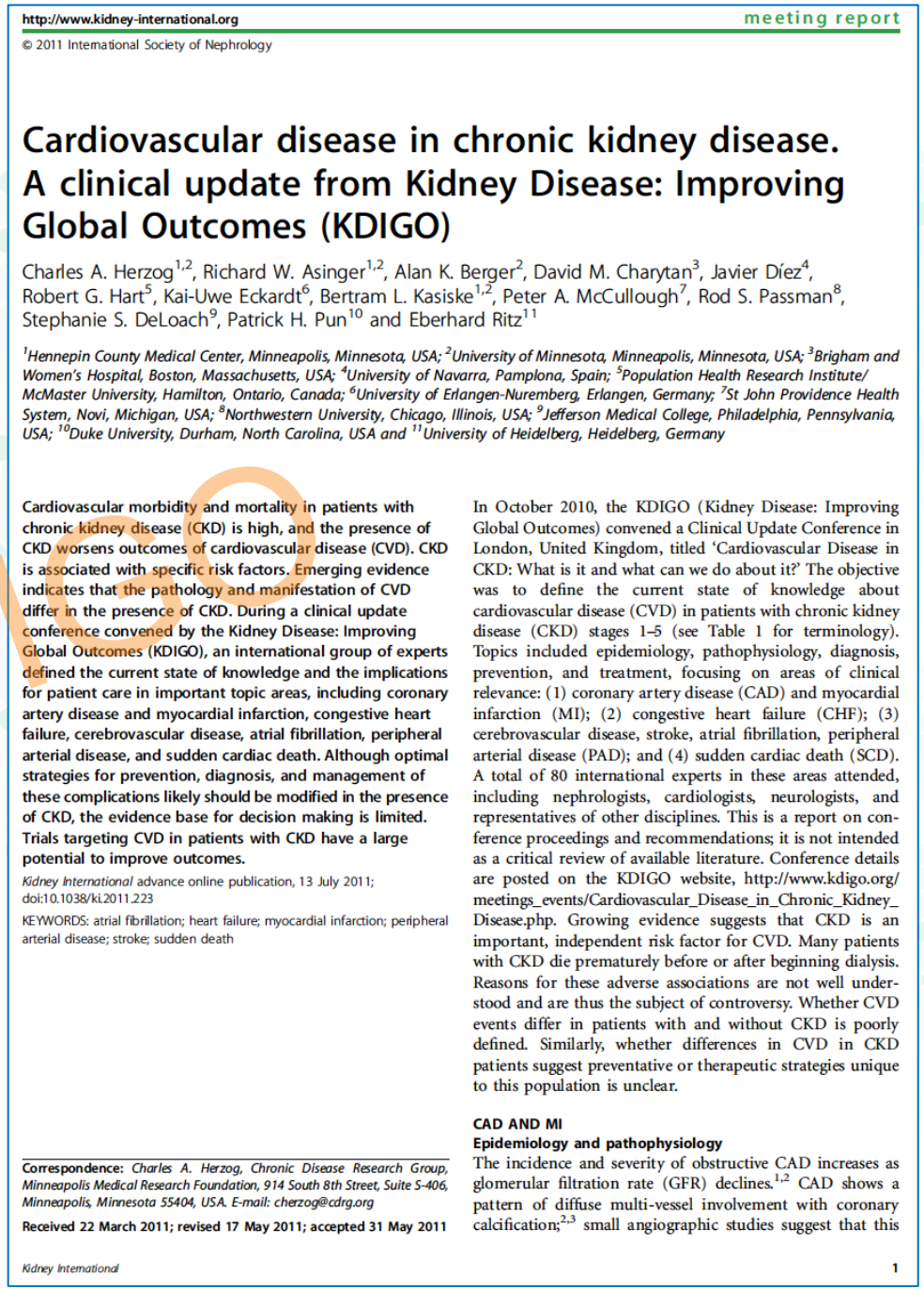
- 12/2009: KDIGO co-chairs ,Profs. Kai-Uwe Eckardt and Bertram Kasiske, invite me and Prof. Eberhard Ritz to co-chair a Controversies Conference entitled "Cardiovascular Disease in CKD: What is it and what can we do about it?" in London (2010).
- Four breakout groups: CAD/MI; CHF, Cerebrovascular Disease/Stroke/AF *and* PAD; Sudden Cardiac Death with 80 attendees
- Equal numbers of nephrologists and cardiologists (!), with additional representation of neurologists and other specialties. Each breakout group was co-chaired by a cardiologist and nephrologist; a neurologist was included for stroke.
- Uniquely valuable experience permitting extended conversations between nephrologists and cardiologists
- *Pirates of the Caribbean: On Stranger Tides* filmed near conference

Cardiovascular Disease in CKD Conference

Held in London in 2010

Conference Report published in *Kidney International* *(718 citations as of 2/3/20).*

Table 1: A Road Map



http://www.kidney-international.org meeting report

Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)

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Cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) is high, and the presence of CKD worsens outcomes of cardiovascular disease (CVD). CKD is associated with specific risk factors. Emerging evidence indicates that the pathology and manifestation of CVD differ in the presence of CKD. During a clinical update conference convened by the Kidney Disease: Improving Global Outcomes (KDIGO), an international group of experts defined the current state of knowledge and the implications for patient care in important topic areas, including coronary artery disease and myocardial infarction, congestive heart failure, cerebrovascular disease, atrial fibrillation, peripheral arterial disease, and sudden cardiac death. Although optimal strategies for prevention, diagnosis, and management of these complications likely should be modified in the presence of CKD, the evidence base for decision making is limited. Trials targeting CVD in patients with CKD have a large potential to improve outcomes.

Kidney International advance online publication, 13 July 2011; doi:10.1038/ki.2011.223

KEYWORDS: atrial fibrillation; heart failure; myocardial infarction; peripheral arterial disease; stroke; sudden death

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In October 2010, the KDIGO (Kidney Disease: Improving Global Outcomes) convened a Clinical Update Conference in London, United Kingdom, titled 'Cardiovascular Disease in CKD: What is it and what can we do about it?' The objective was to define the current state of knowledge about cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) stages 1–5 (see Table 1 for terminology). Topics included epidemiology, pathophysiology, diagnosis, prevention, and treatment, focusing on areas of clinical relevance: (1) coronary artery disease (CAD) and myocardial infarction (MI); (2) congestive heart failure (CHF); (3) cerebrovascular disease, stroke, atrial fibrillation, peripheral arterial disease (PAD); and (4) sudden cardiac death (SCD). A total of 80 international experts in these areas attended, including nephrologists, cardiologists, neurologists, and representatives of other disciplines. This is a report on conference proceedings and recommendations; it is not intended as a critical review of available literature. Conference details are posted on the KDIGO website, http://www.kdigo.org/meetings_events/Cardiovascular_Disease_in_Chronic_Kidney_Disease.php. Growing evidence suggests that CKD is an important, independent risk factor for CVD. Many patients with CKD die prematurely before or after beginning dialysis. Reasons for these adverse associations are not well understood and are thus the subject of controversy. Whether CVD events differ in patients with and without CKD is poorly defined. Similarly, whether differences in CVD in CKD patients suggest preventative or therapeutic strategies unique to this population is unclear.

CAD AND MI

Epidemiology and pathophysiology

The incidence and severity of obstructive CAD increases as glomerular filtration rate (GFR) declines.[1,2] CAD shows a pattern of diffuse multi-vessel involvement with coronary calcification;[2,3] small angiographic studies suggest that this

Condition	Knowledge gaps	Research needs
Atrial fibrillation	• Risks/benefits of anticoagulation with warfarin for stroke prevention • Efficacy, safety of dabigatran in CKD G4 • Uncertainty regarding validity of the 2005 KDOQI guidelines regarding anticoagulation in dialysis patients with atrial fibrillation	• Randomized clinical trials of warfarin and novel anticoagulants for stroke prevention in CKD G4–G5D patients with atrial fibrillation • Interventions to prevent atrial fibrillation: radiofrequency ablation, percutaneous closure of the left-atrial appendage, surgery
SCD	• Standard risk factors derived from the general population may not apply • Few autopsy data • Dialysis patients excluded from primary and secondary prevention trials	• Disease-specific, large-scale prospective cohort studies for risk stratification • Study heterogeneous CKD populations at all stages using all available risk-stratification techniques • Remove barriers preventing data linkage to allow for population-wide cohort and case–control studies • Randomized trials assessing the spectrum of interventions: β-blockers (such as carvedilol), ICDs, sympathetic ablation • Incorporate SCD as specific outcome in registry and clinical trial data. Investigate the potential role of sleep apnea in SCD

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; LV, left ventricular; LVH, LV hypertrophy; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.

Condition	Knowledge gaps	Research needs
CAD, MI	• Screening may be beneficial, but data are insufficient to advocate screening asymptomatic patients • Evidence lacking regarding primary and secondary treatment of CAD • Cardiovascular trials have frequently excluded CKD patients from enrollment	• Clarify the interdependence of CKD with MI, and its relation to demographic characteristics such as gender • Clarify the pathophysiological relationship between development of plaque and subsequent rupture of selected plaques • Clarify roles of novel risk factors that are potential therapeutic targets • Broad-based validation of current stress and imaging modalities using coronary angiography with fractional flow reserve • Adequately powered CKD-specific clinical trials of aspirin, statins, novel anti-lipidemic agents, ACEIs, and ARBs • Define the ideal LDL cholesterol level and the role of newer antiplatelet and anticoagulant therapies • Randomized clinical trials comparing early invasive with conservative therapy post-ACS, and PCI with CABG
CHF	• Understanding development and prevention of LVH, fibrosis, and LV dysfunction (systolic and diastolic) • Benefits of prolonged or quotidian dialysis • Absence of CKD-specific data on CHF treatment • Impact of sodium balance (intake, dialysate sodium concentration)	• Evaluate asymptomatic LV dysfunction, examine changes in the kidney and cardiac function over time, and incorporate kidney- and cardiac-specific biomarkers • Clinical studies to investigate innovative monitoring and management techniques (serial biomarkers, bioimpedance, chronic *in vivo* monitoring) • Evaluate effects of CHF-specific risk-modifying and cardio-protective therapies (ACEIs, ARBs, renin and mineralocorticoid hormone inhibitors) • Investigate speculative treatments (vitamin D analogs/ calcimimetics, cytokine-modulating drugs, iron-related treatments, endothelin receptor blockers, regenerative therapies)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; LV, left ventricular; LVH, LV hypertrophy; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.

Condition	Knowledge gaps	Research needs
Stroke	• High-quality observational data on risk factors, precipitants, etiological subtypes, causes of death, and underlying arteriopathies • Risk of carotid artery stenting is undefined • Few data on treatment of acute stroke	• Randomized clinical trials testing interventions for secondary prevention of stroke • Determine safety of intravenous thrombolysis of CKD G5D patients with acute ischemic stroke
PAD	• Few high-quality observational data on risk factors • Role of ankle–brachial index vs other diagnostic techniques • Prospective data on non-surgical therapies • Data regarding percutaneous vs surgical revascularization	• Determine prevalence of preventive foot care • Assess regional differences in practice patterns • Generate management guidelines • Assess amputation frequency in programs that do and do not perform preventive foot care • Study bacteriology of diabetic patient feet

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; LV, left ventricular; LVH, LV hypertrophy; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.

Cardiovascular Disease in CKD Controversies Conferences: A Brief History (Volume 2)

- 12/2015: I accept a new invitation from KDIGO to help organize a series of CVD/CKD Controversies Conferences modelled on the London 2010 conference, but each with a narrower focus.
- 1/26/2016: KDIGO Co-Chairs, Profs. Wolfgang Winkelmayer and David Wheeler, KDIGO staff, and I meet in the Tangley Room of the Hilton Paddington in London to plan 4 or 5 CVD/CKD Controversies Conferences spanning the next 3 to 5 years.
- Much of the 2010 London conference would be revisited in the light of new knowledge, with new areas of discussion added----with a broad international representation of the nephrology and cardiology communities.
- The overall conference series was entitled “KDIGO Cardiovascular and CKD Conference Series on the Kidney, Heart, and Vasculature”.

CKD & Arrhythmias Conference

Held in Berlin in 10/2016

Sudden Cardiac Death and AF/anticoagulation Highlighted

Report published in the *European Heart Journal*

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 2314–2325
doi:10.1093/eurheartj/ehy060

CURRENT OPINION
Arrhythmia/electrophysiology

Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Introduction

Patients with chronic kidney disease (CKD) are predisposed to heart rhythm disorders, including atrial fibrillation (AF)/atrial flutter, supraventricular tachycardias, ventricular arrhythmias, and sudden cardiac death (SCD). While treatment options, including drug, device, and procedural therapies, are available, their use in the setting of CKD is complex and limited. Patients with CKD and end-stage kidney disease (ESKD) have historically been under-represented or excluded from randomized trials of arrhythmia treatment strategies,[1] although this situation is changing.[2] Cardiovascular society consensus documents have recently identified evidence gaps for treating patients with CKD and heart rhythm disorders.[3–7]

To identify key issues relevant to the optimal prevention, management, and treatment of arrhythmias and their complications in patients with kidney disease, Kidney Disease: Improving Global Outcomes (KDIGO) convened an international, multidisciplinary Controversies Conference in Berlin, Germany, titled *CKD and Arrhythmias* in October 2016. The conference agenda and discussion questions are available on the KDIGO website (http://kdigo.org/conferences/ckd-arrhythmias/; 13 February 2018).

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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† Other conference participants: Kerstin Amann, Germany; Debasish Banerjee, UK; Nisha Bansal, USA; Giuseppe Boriani, Italy; Jared Bunch, USA; Christopher T. Chan, Canada; David M. Charytan, USA; David Conen, Canada; Allon N. Friedman, USA; Simonetta Genovesi, Italy; Rachel M. Holden, Canada; Andrew A. House, Canada; Michel Jadoul, Belgium; Alan G. Jardine, UK; David W. Johnson, Australia; Min Jun, Australia; Laura Labriola, Belgium; Patrick B. Mark, UK; Peter A. McCullough, USA; Thomas D. Nolin, USA; Tatjana S. Potpara, Serbia; Patrick H. Pun, USA; Antonio L. P. Ribeiro, Brazil; Patrick Rossignol, France; Jenny I. Shen, USA; Manish M. Sood, Canada; Yusuke Tsukamoto, Japan; Angela Yee-Moon Wang, Hong Kong; Matthew R. Weir, USA; James B. Wetmore, USA; Jerzy K. Wranicz, Poland; Hiro Yamasaki, Japan.

Heart Failure & CKD Conference

Held in Athens in 5/2017

Report published in *Kidney International*

Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Check for updates

OPEN

Andrew A. House[1], Christoph Wanner[2], Mark J. Sarnak[3], Ileana L. Piña[4], Christopher W. McIntyre[5], Paul Komenda[6,7,8], Bertram L. Kasiske[9], Anita Deswal[10,11], Christopher R. deFilippi[12], John G.F. Cleland[13,14], Stefan D. Anker[15,16,17], Charles A. Herzog[18,19], Michael Cheung[20], David C. Wheeler[21], Wolfgang C. Winkelmayer[22] and Peter A. McCullough[23,24]; for Conference Participants[25]

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The incidence and prevalence of heart failure (HF) and chronic kidney disease (CKD) are increasing, and as such a better understanding of the interface between both conditions is imperative for developing optimal strategies for their detection, prevention, diagnosis, and management. To this end, Kidney Disease: Improving Global Outcomes (KDIGO) convened an international, multidisciplinary Controversies Conference titled *Heart Failure in CKD*. Breakout group discussions included (i) HF with preserved ejection fraction (HFpEF) and nondialysis CKD, (ii) HF with reduced ejection fraction (HFrEF) and nondialysis CKD, (iii) HFpEF and dialysis-dependent CKD, (iv) HFrEF and dialysis-dependent CKD, and (v) HF in kidney transplant patients. The questions that formed the basis of discussions are available on the KDIGO website http://kdigo.org/conferences/heart-failure-in-ckd/, and the deliberations from the conference are summarized here.

Kidney International (2019) **95,** 1304–1317; https://doi.org/10.1016/j.kint.2019.02.022

KEYWORDS: cardiovascular disease; chronic kidney disease; congestive heart failure; hemodialysis; transplantation

HF and CKD represent concurrent chronic disease epidemics.[1,2] Both conditions have increasing incidence and prevalence in older age groups as well as persons with hypertension, diabetes mellitus, or other cardiovascular and kidney disease risk factors.[3] The presence of one condition appears to accelerate the presentation and progression of the other; having both conditions increases the risk of hospitalization, rehospitalization, need for intensive care or kidney replacement therapy, and death.[4–9] In addition, patients with HF and CKD may fail to respond as predicted to conventional therapies or experience increased toxicity to them.[10,11]

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[25]See Appendix for list of other conference participants.

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Coronary Artery & Valvular Diseases in CKD Conference

Held in Vienna in 6/2018

VHD Report published in *Kidney International*

CAD Report published in *JACC*

KDIGO executive conclusions www.kidney-international.org

Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Check for updates

Thomas H. Marwick[1,18], Kerstin Amann[2], Sripal Bangalore[3], João L. Jonathan C. Craig[6], John S. Gill[7], Mark A. Hlatky[8], Alan G. Jardine[9], Charles A. Herzog[12,13], Michael Cheung[14], David C. Wheeler[15], Wo Mark J. Sarnak[17,18]; for Conference Participants[19]

[1]Imaging Research Lab, Baker Heart and Diabetes Institute, Melbourne, Victoria, Austra Hospital Erlangen, Germany; [3]Division of Cardiology, New York University School of M and Structural CT and Cardiovascular Imaging Core Lab, Minneapolis Heart Institute, Nephrology, New York University School of Medicine, New York, New York, USA; [6]Colle University, Adelaide, Australia; [7]Division of Nephrology, St. Paul's Hospital, University o Canada; [8]Department of Health Research and Policy, Stanford University School of Me Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [10]Departme Berlin, Germany; [11]Division of Cardiology, Department of Medicine and Duke Clinical Re Durham, North Carolina, USA; [12]Division of Cardiology, Department of Medicine, Henr Minnesota, Minneapolis, Minnesota, USA; [13]Chronic Disease Research Group, Minneap Minnesota, USA; [14]KDIGO, Brussels, Belgium; [15]Centre for Nephrology, University Colleg Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Med Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts, US

Chronic kidney disease (CKD) is a major risk factor for valvular heart disease (VHD). Mitral annular and aortic valve calcifications are highly prevalent in CKD patients and commonly lead to valvular stenosis and regurgitation, as well as complications including conduction system abnormalities and endocarditis. VHD, especially mitral regurgitation and aortic stenosis, is associated with significantly reduced survival among CKD patients. Knowledge related to VHD in the general population is not always applicable to CKD patients because the pathophysiology may be different, and CKD patients have a high prevalence of comorbid conditions and elevated risk for periprocedural complications and mortality. This Kidney Disease: Improving Global Outcomes (KDIGO) review of CKD and VHD seeks to improve understanding of the epidemiology, pathophysiology, diagnosis, and treatment

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The conference agenda, discussion questions, and plenary session presentations are available on the KDIGO website: https://kdigo.org/conferences/controversies-conference-on-coronary-artery-valvular-disease/.

[18]THM and MJS are primary co-authors.

[19]See Appendix for list of other Conference Participants.

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of VHD in CKD
controversy, and
Kidney International
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KEYWORDS: aortic s
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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 14, 2019

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Chronic Kidney Disease and Coronary Artery Disease

***JACC* State-of-the-Art Review**

Mark J. Sarnak, MD, MS,[a] Kerstin Amann, MD,[b] Sripal Bangalore, MD, MHA,[c] João L. Cavalcante, MD,[d] David M. Charytan, MD, MSc,[e] Jonathan C. Craig, PhD,[f] John S. Gill, MD, MS,[g] Mark A. Hlatky, MD,[h] Alan G. Jardine, MD,[i] Ulf Landmesser, MD,[j] L. Kristin Newby, MD, MHS,[k] Charles A. Herzog, MD,[l,m] Michael Cheung, MA,[n] David C. Wheeler, MD,[o] Wolfgang C. Winkelmayer, MD, MPH, ScD,[p] Thomas H. Marwick, MBBS, PhD, MPH,[q] for Conference Participants*

ABSTRACT

Chronic kidney disease (CKD) is a major risk factor for coronary artery disease (CAD). As well as their high prevalence of traditional CAD risk factors, such as diabetes and hypertension, persons with CKD are also exposed to other nontraditional, uremia-related cardiovascular disease risk factors, including inflammation, oxidative stress, and abnormal calcium-phosphorus metabolism. CKD and end-stage kidney disease not only increase the risk of CAD, but they also modify its clinical presentation and cardinal symptoms. Management of CAD is complicated in CKD patients, due to their likelihood of comorbid conditions and potential for side effects during interventions. This summary of the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on CAD and CKD (including end-stage kidney disease and transplant recipients) seeks to improve understanding of the epidemiology, pathophysiology, diagnosis, and treatment of CAD in CKD and to identify knowledge gaps, areas of controversy, and priorities for research. (J Am Coll Cardiol 2019;74:1823-38) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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KDIGO Central and Peripheral Arterial Disease Conference: Dublin, 2020

- Originally entitled "Non-Coronary Vascular Disease"
- Breakout groups: aortic, cerebrovascular, renovascular, and peripheral arterial disease
- Interventional Radiologists represented (first time) with other specialties

Thanks to everyone attending the "final" KDIGO Cardiovascular and CKD Conference on the Kidney, Heart, and Vasculature.

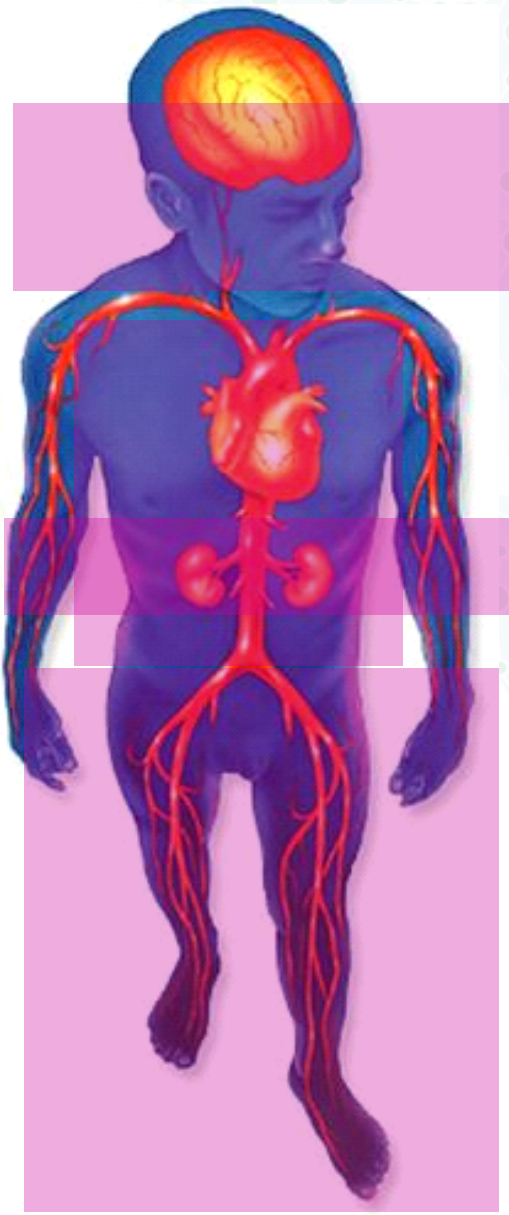
(Let's work on the road map for the next decade).

KDIGO Controversies Conference on Central & Peripheral Arterial Diseases in CKD

February 21-23, 2020

Dublin, Ireland

Agenda and Aims



Cerebrovascular Atherosclerotic Disease (except intracerebral)

Aortic Disease (from root to bifurcation)

Renovascular Disease

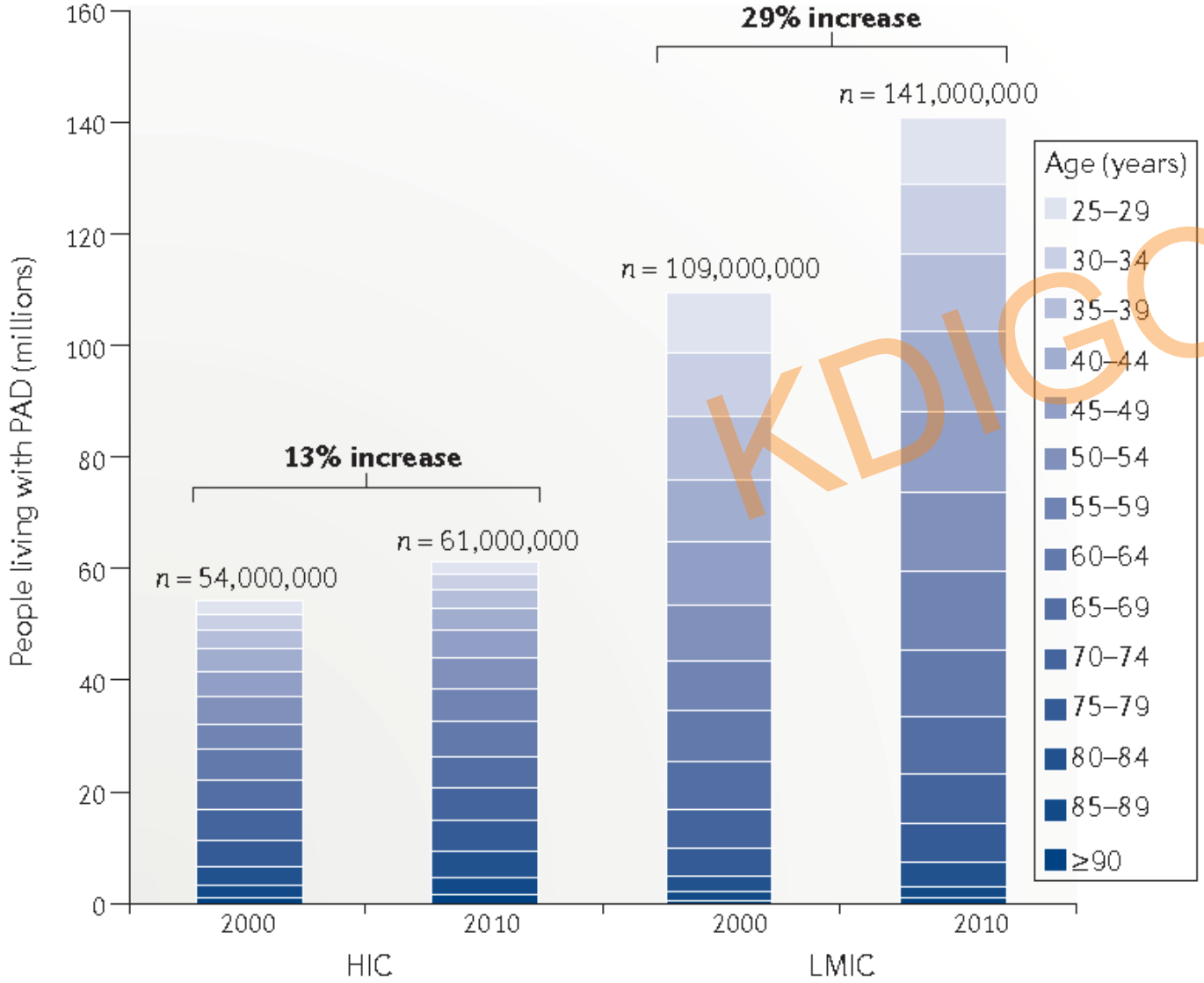
Lower Limb Atherosclerotic Disease

Epidemio-logy	Pathology	Management (diagnostics and therapy)	Special issues
			Acute Kidney Injury
			Fibromusc-ular Dys-plasia (FMD)

THE GOAL OF THIS KDIGO CONFERENCE IS …

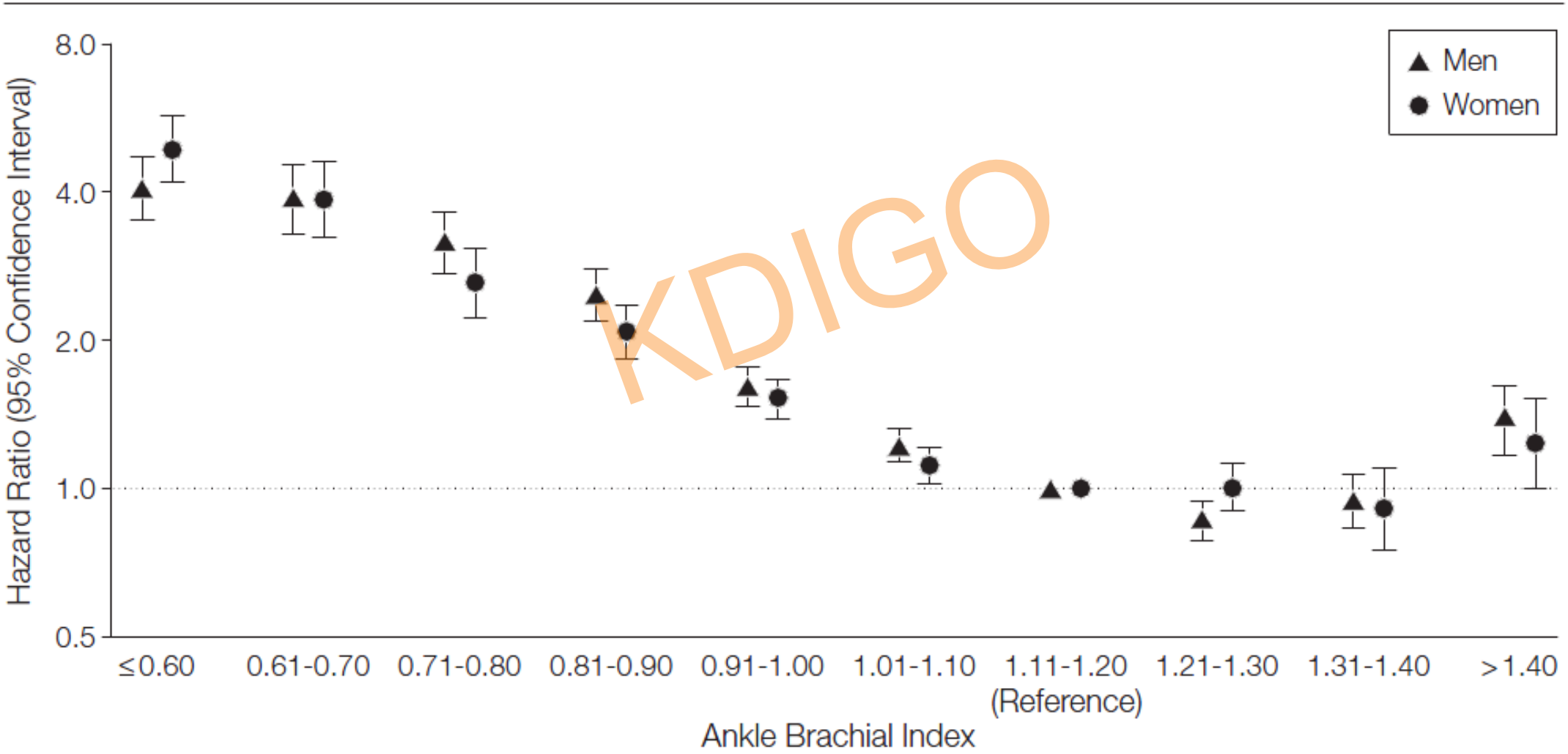
- to determine best practice and summarize areas of uncertainty
- review key relevant literature
- address ongoing controversial issues
- and propose a research agenda to address any gaps in knowledge.

E.G. LOWER LIMB ATHEROSCLEROTIC DISEASE: EPIDEMIOLOGY



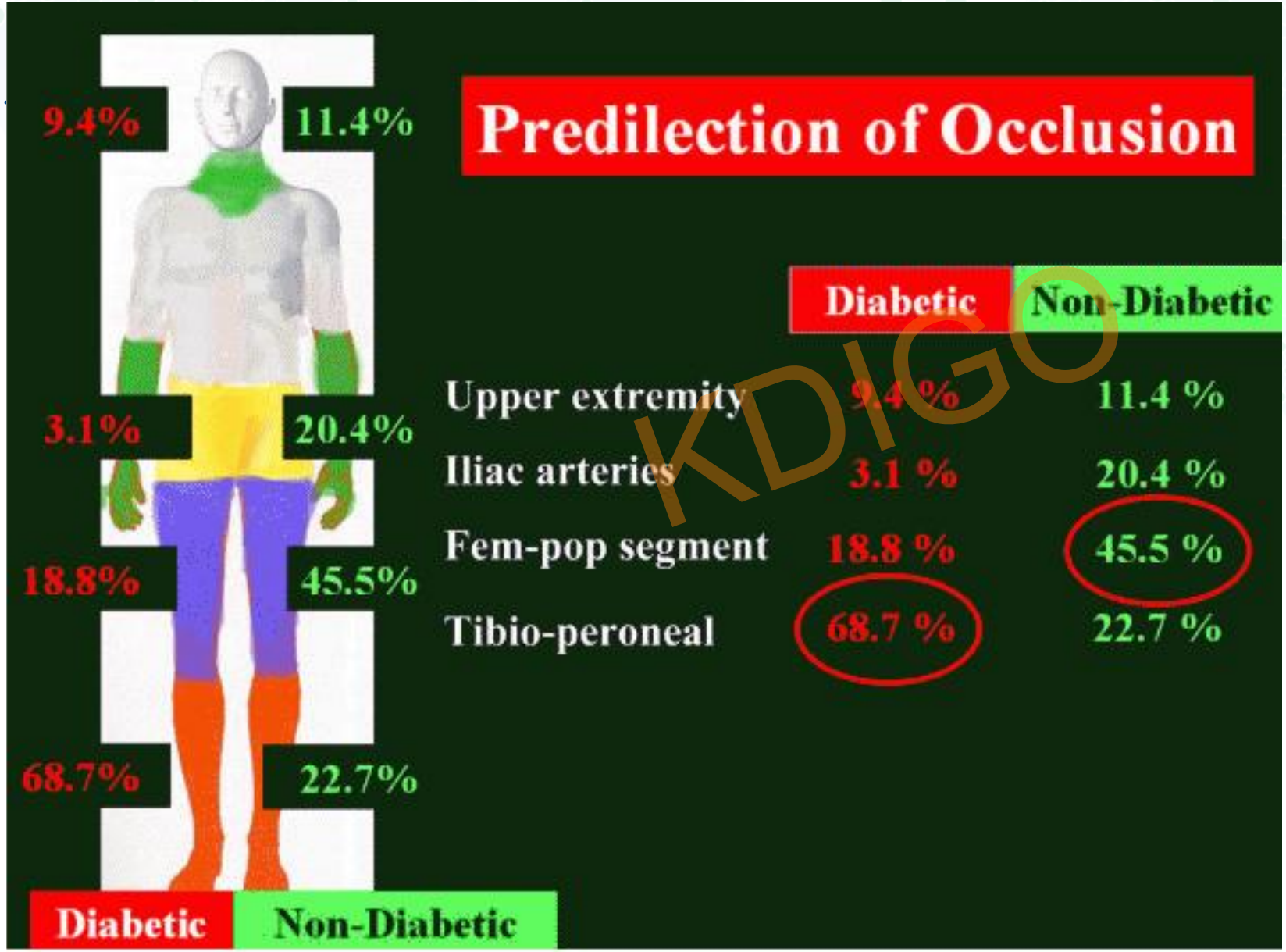
Fowkes FG et al.
Nat Rev Cardiol. 2016 Nov 17

E.G. Lower Limb Atherosclerotic Disease: Diagnostics

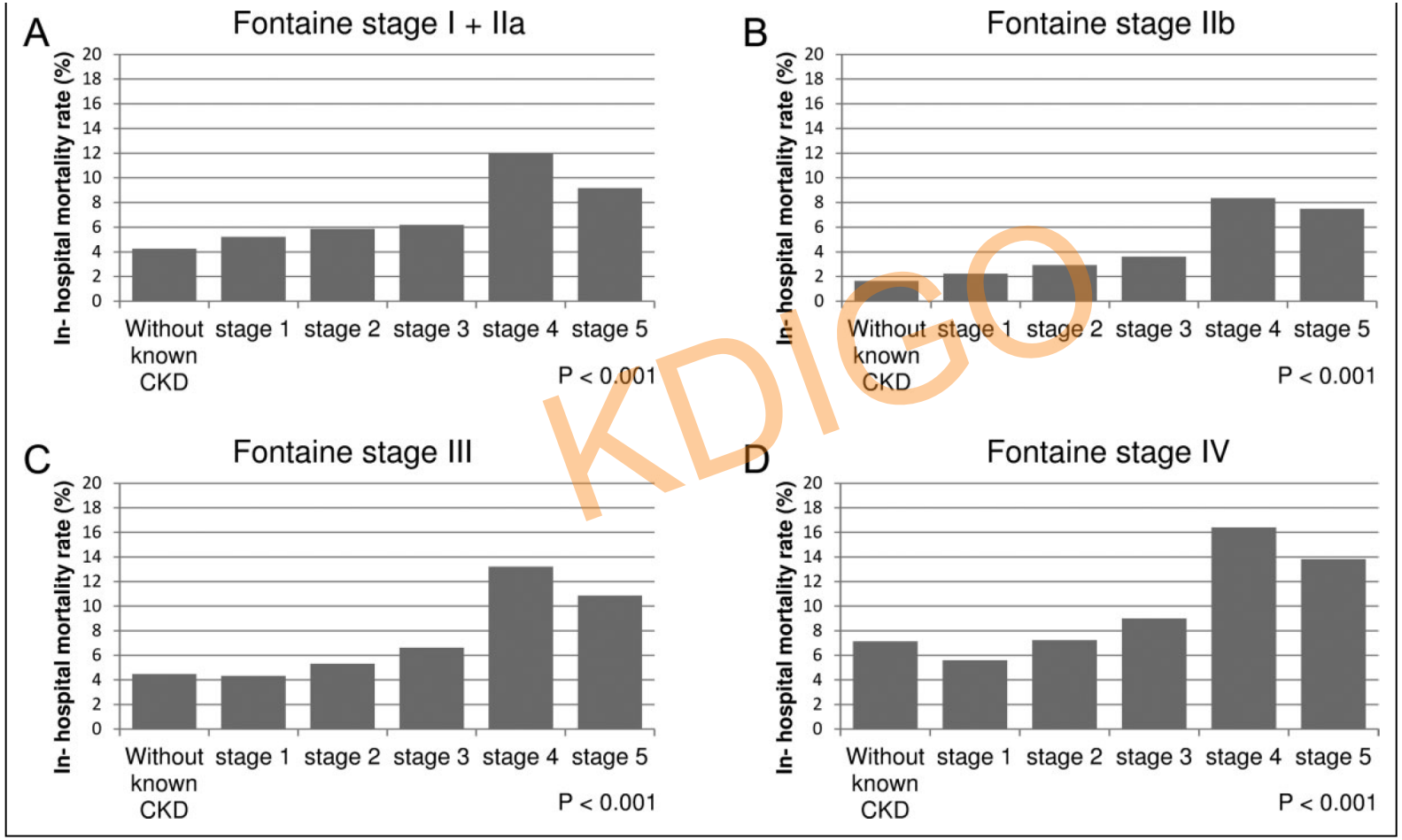


Fowkes G et al. JAMA. 2008;300:197-208

Type and Location of PAD



E.G. Lower Limb Atherosclerotic Disease: Inhospital Outcomes

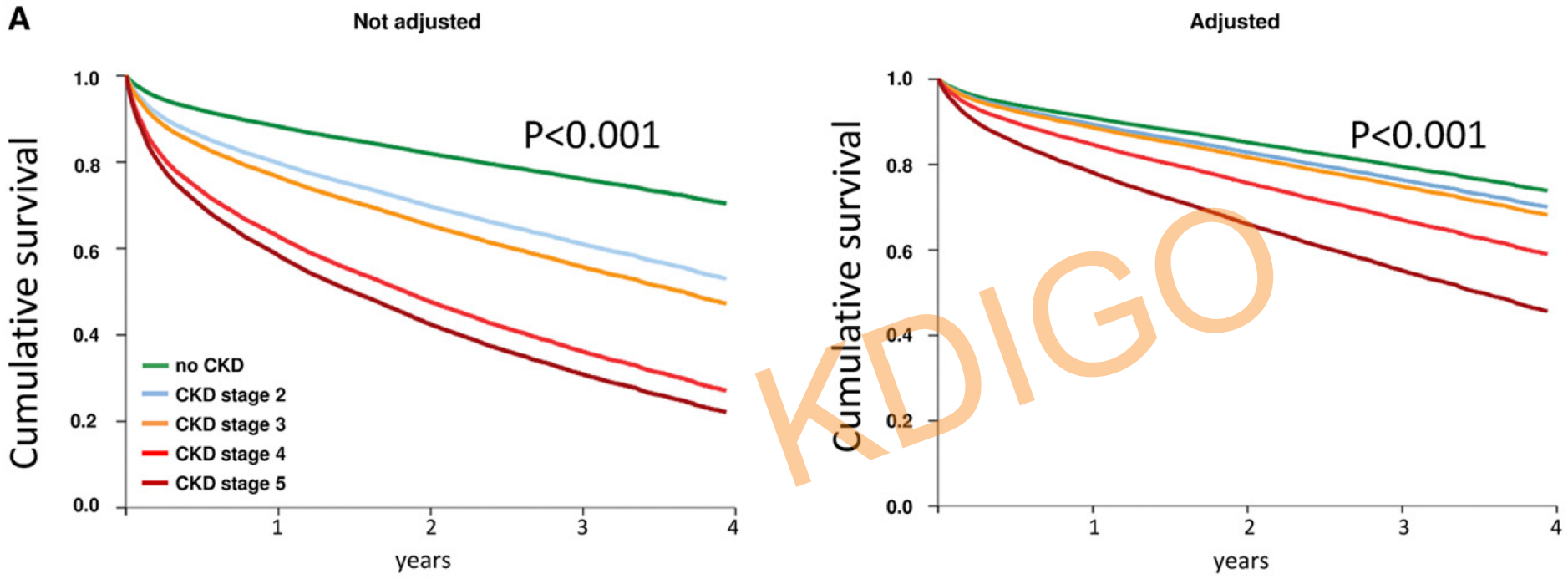


Data from 2009: 483 961 patients. Of those, 132 993 (27.5%) had CKD.

Figure 2. In-hospital mortality among hospitalized patients having peripheral arterial disease (PAD) without and with known chronic kidney disease (CKD).

Lüder F et al. Angiology 1-6; 2016: DOI: 10.1177/0003319716638797

E.G. Lower Limb Atherosclerotic Disease: Longterm Outcomes



no CKD	29,162	18,701	9,285	6
CKD stage 2	1,715	1,124	597	0
CKD stage 3	2,959	1,707	766	0
CKD stage 4	572	289	116	0
CKD stage 5	797	410	183	0

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CKD stage 5	797	410	183	0

Data from 2009-2012:
41,882 patients.
Of those,
8,470(20.2%) had CKD.

Lüders F et al. Clin J Am Soc Nephrol 11: 2016. doi: 10.2215/CJN.05600515