Arjona Barrionuevo Jde D, Gonzales Vargas-Machuca M, Guerrero Márquez FJ, Gil-Sacaluga L, Gentil-Govantes MA. Utility of A Cardiorenal Monographic Consultation to Reduce The Cardiovascular Mortality of The Renal Transplant Patient. J Cardiol and Cardiovasc Sciences. 2019;3(3):1-8

Journal of Cardiology and Cardiovascular Sciences

Original Research Article

Open Access

Utility of A Cardiorenal Monographic Consultation to Reduce The Cardiovascular Mortality of The Renal Transplant Patient

Juan de Dios Arjona-Barrionuevo[1], Manuel Gonzales Vargas-Machuca[2], Francisco José Guerrero-Márquez[3]*, Luis Gil-Sacaluga[4], Miguel Ángel Gentil-Govantes[4]

[1]Department of Cardiology, Hospital University Virgen del Rocio, Seville, Spain

[2]Departament of Cardiology, Hospital San Juan de Dios del Aljarafe, Bormujos (Seville), Spain

[3]Department of Cardiology, Hospital de la Serrania Ronda, Spain

[4]Department of Nephrology, Hospital University Virgen del Rocio, Seville, Spain

Article Info

Article Notes
Received: April 13, 2019
Accepted: May 22, 2019

***Correspondence:**
Dr. Francisco José Guerrero Márquez, C/ Cervantes 25, Olvera (Cádiz) 11690. Spain; Telephone No: +34627430503; Email: guerreromar24@gmail.com.

Keywords
Cardiovascular mortality
Renal transplantation
Coronary revascularization

Abstract

Introduction and objectives: WHO recognizes chronic kidney disease as a serious health problem with increasing incidence and prevalence. In our midst, the first cause of death in renal replacement therapy is cardiovascular disease (CVD), especially ischemic. We studied and follow-up of candidates for renal transplantation and subsequently transplanted, With the objective of knowing the ischemic load and reducing the mortality of the transplant.

Methods: In November 2005, we began a cardiorenal monographic consultation for the study of all patients with chronic renal disease with a high cardiovascular risk who were candidates for renal transplantation who underwent coronary angiography, according to the protocol prior to transplantation, were studied.

Results: From November 2005 to December 2013, 313 patients were studied, 64% males, 56.7 ± 11 years old. The Prevalence of significant coronary lesions: 39.3%, 54.4, % of more than one vessel. Silent: 32.4%, 47.6% more than one glass. Total mortality of candidates: 10.2%. Cardiovascular: 4.8%. Total transplant mortality: 5.3%, cardiovascular: 2.1%. Cardiovascular mortality of the revascularized transplant patient: 0%.

Conclusions: Screening and intervention on CVD, leven preventive, reduce total and cardiovascular mortality of the transplant, extending this benefit to those remaining on dialysis. In our hospital, CVD is no longer the leading cause of death in renal replacement therapy.

Introduction

Chronic kidney disease (CKD) is recognized by the World Health Organization (WHO) as a serious health problem, with a prevalence of approximately 10% according to various epidemiological studies[1-5]. This prevalence is expected to increase in the coming years[6]. Many cases remain undiagnosed due to the absence of symptoms; these cases constitute occult renal disease, and as the disease becomes chronic, the prognosis worsens[7,8].

CKD is closely associated with several pathologies that are increasingly prevalent and have reached epidemic levels in developed countries, including high blood pressure (HBP), obesity, diabetes mellitus or even aging[9]. This association increases the cardiovascular risk of these patients, which promotes the development of cardiovascular diseases and further worsens the prognosis. Advanced stage of CKD are directly associated with a greater burden of arteriosclerosis, including coronary artery disease, to the point that more than 50% patients undergoing

kidney replacement therapy die due to cardiovascular complications. Cardiovascular mortality is the main cause of death in patients undergoing any type of kidney replacement therapy, as well as the first cause of loss of a functioning allograft in transplant patients[10,11].

In an attempt to reduce cardiovascular mortality, several groups have carried out screening studies of ischemic heart disease in patients undergoing kidney replacement therapy or prior to kidney transplantation[12,13], with beneficial effects and promising results.

Hoping to increase survival, the American Transplant Society[14] and the Integrated Care Process of Kidney Replacement Therapy of the Andalusian Community have recommended that candidates for kidney transplantation who are at high cardiovascular risk, including asymptomatic patients, should undergo screening for myocardial ischemia.

Since 2005, our center has provided cardiology consultation services in order to detect cardiovascular pathology in patients who are candidates for kidney transplantation. For more than 13 years, the purpose of such consultations has been to decrease cardiovascular mortality in transplant patients, which is the leading cause of loss of a functioning allograft.

Materials and Methods

Protocol and patients

In November 2005, a protocol was established between the Department of Nephrology and Department of Cardiology of the Virgen Rocio Hospital, Seville, for the study and screening of ischemic heart disease in patients eligible for high-risk cardiovascular transplantation. Consultation included a clinical assessment of the patient and ordering of appropriate cardiac ischemia tests, including invasive studies such as coronary angiography. Once they were enrolled, those patients who received transplants and those who remained on dialysis for whatever reason were monitored in the clinic.

The study protocol included the completion of a detailed clinical history, electrocardiogram, blood tests and echocardiograms for all patients. Tests for ischemia detection (Ergometry[15]), Perfusion scintigraphy with Tc 99[16] and Stress echocardiography with dobutamine[17]) were carried out in asymptomatic patients according to clinical practice guidelines but allowing for some individualization depending on the characteristics of each patient. Angiographic studies were performed in patients with typical angina, those who had a documented history of heart disease (despite being asymptomatic), and those with a positive or concerning result on one of the ischemia detection tests. Angiography was also performed in patients with a high cardiovascular risk, such as diabetic patients with a prolonged history of vascular complications, participants with demonstrated general atherosclerosis or those with left ventricular systolic dysfunction, regardless of their symptoms and the results of the ischemia induction tests.

The angiographic studies were carried out following a rigorous and exhaustive protocol aimed at minimizing the risk of secondary complications. All patients were previously assessed by a nephrologist in preparation for the transplant and during follow-up, until discharge from the hospital. Patients undergoing kidney replacement therapy underwent a dialysis session after catheterization at the discretion of the nephrologist. The patients who were not yet on dialysis received nephroprotective interventions consisting in the withdrawal of nephrotoxic drugs and the administration of saline, 1/6M sodium bicarbonate and oral N-acetyl cysteine.

All the coronary angiograms were performed via the femoral approach in order to preserve the arteries of the arms in the event of possible fistula placement. The usual projections of the coronary tree were obtained; the images were stored digitally and were interpreted by our cardiologists. The indication for revascularization was decided upon jointly by the cardiologist caring for the patient and the cardiologist performing for the procedure. In the case of significant coronary lesions in asymptomatic patients, the decision was made based on the severity and location of lesions. In suspect cases, the decision was made according to whether there was ischemia on previous testing that indicated a significant area of ischemic myocardium or according to the readings of the pressure guidewire. Significant coronary lesions were revascularized percutaneously, except for cases involving intractable lesions, poor distal vessels or very distal lesions. Surgical revascularization was indicated in patients with multivessel lesions and/or left main lesions, as outlined in clinical practice guidelines[18]. Decisions were always made on consensus during meetings with both medical and surgical specialists (*Heart Team*).

The antiplatelet treatment used in patients who were implanted with endovascular devices (stents*)* was acetylsalicylic acid (ASA) and clopidogrel. Dual antiplatelet therapy was continued for 6 months in patients who received a metallic or conventional stent and for one year in patients with a drug-eluting stent. Patients were temporarily excluded from the waiting list for kidney transplantation while they were on dual antiplatelet therapy. It must be considered that the devices implanted during the first years of the study were first-generation *drug-eluting* stents, which is why the recommendations for dual antiplatelet therapy duration are different from current recommendations based on newer evidence.

The clinical follow-up of the patients was carried out in the same clinic cardiologist where the study was started; thus, the same clinical cardiologist monitored a

given patient's course. Patients without any evidence of heart disease were monitored annually, while those who underwent revascularization were followed up at one month, six months, and one year. The management and control of cardiovascular risk factors during follow-up was an essential component of these patients' care. Treatment was optimized in accordance with European clinical practice guidelines; patients received ASA, statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARA-II) and Beta blockers[19-21].

Definitions

High cardiovascular risk of the population with advanced CKD is defined by the presence of one or more of the risk factors listed in *Table 1*. All the patients who were followed by our consultation service were considered to have high cardiovascular risk. Corrected age is defined as the chronological age plus the time that the patient has been on dialysis.

Significant coronary lesions are defined as those causing a reduction of >75% of the luminal diameter of an epicardial vessel (vessel with a diameter above 1.5 mm) or >50% if the location is the left main coronary[22]. In cases in which the angiographic interpretation was in doubt, lesions were assessed by intravascular ultrasound (IVUS) or by pressure guidewires (fractional flow reserve, FFR).

Occult coronary disease is defined as the presence of significant coronary lesions in asymptomatic patients.

Cardiac events during follow-up were defined as the appearance of an acute coronary syndrome (unstable angina or acute myocardial infarction with or without ST-segment elevation) or sudden death (unexpected death less than 1 hour after onset of symptoms). We assumed that all sudden death that was unexplained was cardiac in etiology, despite the high frequency of ion channel disorders in these patients. Vascular events refer to the occurrence of ischemic or hemorrhagic cerebral vascular accidents during follow-up.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Values of $p<0.05$ were considered statistically significant. The differences between groups were analyzed using ANOVA and chi-squared tests as appropriate. All the statistical analyses were performed with the software SPSS, version 16.0 for Windows.

Ethics statement

The authors declare that all humans involved in this study were treated in a manner in accordance with the Declaration of Helsinki and the Declaration of Istanbul. Our study was exempt from approval from an ethics' board.

Results

From November 2005 to December 2013, we studied 313 patients candidates for kidney transplant, who underwent coronary angiography, of whom 94 eventually underwent transplantation. The demographic clinical characteristics of the study population are shown in *Table 2*. Patients were predominantly male (200 of 313 (64%)) and of almost exclusively Caucasian race (99%). Hypertension was the most prevalent cardiovascular risk factor (96%). Almost two thirds of the patients were diabetic, with diabetic nephropathy accounting for almost 20% of the causes of CKD. Of the 313 patients, 39 had a prior diagnosis of ischemic heart disease (12%). The high prevalence of smoking among the study participants is striking (56%). It is important to note that 86% of participants did not have any cardiac symptoms. The most common symptoms were chest pain and dyspnea on exertion.

The mean duration of renal replacement therapy was 1.1 years (0.2 - 4.9 years), with hemodialysis being the most prevalent modality. The main causes of acute CKD (ACKD) were glomerulonephritis, diabetic nephropathy and vascular nephropathy.

The sensitivity and specificity of the various ischemia detection tests are shown in *Table 3*. Most tests

Table 1. High cardiovascular risk

1.- Coronary artery disease documented
2.- Symtomatic typical angina or anginal equivalent
3.- Asyntomatics patients with one of the following features:
a.- Age "corrected"(chronological age plus years corrected in SRT) above 55 years
b.- Age corrected between 35-55 years and 2 or more clasic risk factors
- Family history of early coronary artery disease
- Dyslipidemia
- Hypertension.
- Active smoking or ex-smoker of ≥10 cigarettes
- Non-coronary atherosclerotic disease demonstrated
4.-Diabetes Mellitus
5.- LVEF <50%

Table 2. Clinical Characteristics of the population

n = 313	Nº / %
Age, years	56.7 ± 11
Male	200 (64%)
White race	310 (99%)
Hypertension	300 (96 %)
Dyslipidemia	196 (62.6%)
Smoking	178 (56.8%)
Diabetes	98 (31.3%)
Prior coronary artery disease	39 (12.6%)
Cerebrovascular disease.	30 (9.7%)
Peripheral artery disease.	54 (17.4%)
LVEF < 50%.	25 (7.9%)
Left ventricular hypertrofy	227 (72.6%)
Causes of chronic kidney disease	
Glomerulonephritis.	76 (24.2%)
Diabetes.	61 (19.5%)
Hypertension/ Vascular.	41 (13.1%)
Nephropathy tubular.	37 (11.8%)
Polycystic kidney disease.	31 (10%)
Others	67 (21,4%)
Sustitutive renal therapy	
Hemodialysis.	275 (87,8%)
Peritoneal dialysis	18 (5,7%)
Pre-dialysis.	20 (6.3%
Time in sustitutive renal therapy.	1.1 (0.28 / 4.9) years
Syntoms	
Asyntomatic	262 (86%)
Angina	16 (5%)
Chest pain	17 (5.8%)
Others (dyspnoea, palpitations)	18 (5,4)%

Table 3. Comparison of sensitivity and specificity

AKCD	Ergometry	Stress echo	Spect exercise	Spect adenosine
Sensitivity	35%	65%	43%	87%
Specificity	64%	80%	64%	60%
GENERAL	**Ergometry**	**Stress echo**	**Spect exercise**	**Spect adenosine**
Sensitivity	65%	85%	75%	88%
Specificity	70%	95%	80%	73%

Comparison of sensitivity and specificity values of the ischemia detection tests between the general population and patients with ACKD in our study.

had a lower sensitivity and specificity in patients with CKD than in the general population, except myocardial perfusion scintigraphy with pharmacological stress (adenosine SPECT), which had somewhat similar sensitivity (87% vs 88%) but lower specificity (60% vs 73%).

Results of coronary angiography

As shown in *Table 4*, the prevalence of significant coronary lesions found on catheterization was high (123 of 313 patients (39.3%)), and all lesions had some component of calcification to varying extents (diffuse lesions: 51%; focal lesions: 49%).The prevalence of occult coronary disease was 32.4%; of these, 27% had negative ischemia detection tests.

Table 4. Coronary angiography results

Coronary angiography nº 313p	Nº pacients	%
Any lesions	150	48
Obstructive lesions	163	52
SIGNIFICANT CORONARY LESIONS	123	39,3
Type of lesions		
Monovase	56	45,5
Two vases	26	21.1
Multivase	41	33.3
SILENT CORONARY LESIONS	**40**	**32.4**
Type of lesions		
Monovase	21	52.3
Two vases	7	17.4
Multivase	12	30.2

Of the 123 patients with significant coronary lesions, 83 (67.4%) underwent revascularization; most revascularization was percutaneous (96.2%), and only 4% of patients required surgical revascularization (2 patients with left main lesions and another 2 with multivessel disease and involvement of the proximal descending artery). Forty patients (32.5%) were considered non-revascularizable, either because they had technically unapproachable lesions or due to high surgical risk or poor distal vessels; for such patients, the adjustment of conservative treatment as the only therapeutic possibility. Regarding the type of stent implanted, in the first years of the study conventional stents were used (30 patients). With the later development of drug-eluting stents, these stents were implanted in 40 patients. Nine patients received a combination of drug-eluting and conventional stents.

It should be noted that complications related to catheterization were rare (<1%), and they mainly involved local complications at the puncture site (4 patients developed a pseudoaneurysm, one of which resolved spontaneously; two were implanted with stents and one required surgical closure by vascular surgery). None of the patients who were in the predialysis stage at the time of coronary angiography developed contrast nephropathy, and there were no other complications related to percutaneous revascularization in those undergoing renal replacement therap. A periprocedural infarction and a subacute restenosis of one of the conventional stents occurred, and both resolved satisfactorily. The rate of clinical restenosis of the stents was 7% (6 patients), with no differences according to the type of implanted device.

Exclusion of transplant candidates

The exclusion criteria for transplantation are shown in *Table 5*: severe cardiac dysfunction (LVEF<30%), especially ischemic dysfunction, the presence of significant non-revascularizable multivessel or single-vessel coronary lesions with moderate to severe ischemia on screening tests, and the presence of severe uncorrected valvular heart disease. Based on these criteria, a total of 24 patients (7.6%) were excluded; these were mainly patients who were not candidates for coronary revascularization and had severe ischemia.

Mortality analysis

Table 6 shows the mortality outcomes during follow-up (24 months +-15 months) for all patients studied in the clinic, transplant patients, and patients who underwent revascularization (regardless of whether they received a transplant). Total mortality was 10%, with cardiovascular causes accounting for half of the deaths. With regard to the main focus of the study, mortality in transplant patients from any cause was 5.3% (5 patients), with only 2 deaths of cardiovascular etiology (due to heart failure). The cardiovascular mortality of transplant patients who underwent revascularization was 0%.

Table 5: Pacients excluded from kidney trasplantation

Cause of exclusion	Nº Patients (24)	Mortality
Not revascularizables	17	7
LVEF <30%	5	0
Several valvular heart disease	2	2

Mortality of 313 studied patients	Nº	%
Total mortality	32	10.2
Cardiovascular	15	4.8
Cardiac	9	2.8
Vascular	6	1.9
Mortality of 94 trasplanted pacients	**Nº**	**%**
Total mortality	5	5.3
Cardiovascular	2	2.1
Cardiac	2	2.1
Vascular	0	0
Mortality of 83 revascularized pacients	**Nº**	**%**
Total mortality	8	9.6
Cardiovascular	4	4.8
Cardiac Acute coronary syndrome: 0p Sudden death: 1p Others: 1p	2	2.4
Vascular Ischemic cerebrovascular event: 1p Intracerebral haemorrhage: 1p	2	2.4
Mortality trasplanted revascularized (24p)	**Nº**	**%**
Total mortality	1	4.1
Cardiovascular	0	
Cardiac Sudden death	0 0	
Cerebrovascular Mortality	0	
Mortality revascularized in dialysis (59p)	**Nº**	**%**
Total mortality	7	11.8
Cardiovascular	4	6.7

Table 6. Mortality analysis of the patients studied, and disaggregated in transplanted patients and those revascularized regardless of whether they were transplanted or not.

Discussion

The main purpose of the study was to assess the burden of cardiovascular disease, especially ischemic disease, in our population of transplant candidates at high cardiovascular risk. We also aimed to decrease cardiovascular mortality among transplant patients, as cardiovascular disease is the leading cause of loss of a functioning allograft in our setting. The prevalence of ischemic heart disease in our study was high (39.3%); it was even higher than in the series published by Kumar et al.[13], in which it was approximately 28%, but was somewhat lower than in the study by Ohtake et al.[23], in which case it exceeded 50%. In addition, in more than half of the cases (54.4%), the demonstrated coronary lesions involved more than one vessel and all of them had some degree of calcification. Considering that the average duration of renal replacement therapy slightly exceeds one year, this result suggests that the progression of coronary atherosclerosis begins in stages of disease that precede inclusion in dialysis programs. Therefore, carrying out screening for ischemic heart disease at earlier stages of CKD (stage 3-4) would allow for earlier diagnosis and the initiation of an optimal treatment regimen to delay the progression of coronary disease, with pharmacological adjustment and coronary revascularization if appropriate. Early invasive management is not associated with an increase in the rate of complications inherent to catheterization, as reflected in this and other studies. The overall rate of complications did not exceed 1%. Most complications involved the puncture site, and all of them resolved without any mortality. One controversial point is the possibility that coronary angiography may accelerate the initiation of renal replacement therapy in those patients who are in predialysis stages of CKD. Kumar et al.[24] found that coronary angiography screening in predialysis patients did not accelerate the initiation of dialysis. These results that are comparable to ours, as we did not observe any case of contrast-induced nephropathy or cholesterol embolization, and there was no accelerated initiation of dialysis.

In contrast to the general population, the presence or absence of anginal symptoms was a poor indicator of coronary disease in our patients, as 86% of them were asymptomatic (*Table 2*), but 32% in the asymptomatic

group had significant coronary lesions. This important result is in agreement with the percentage of asymptomatic patients with coronary lesions reported in a previous study[13], although the value in that study was somewhat higher (54%). The absence of symptoms cannot be explained solely by the autonomic neuropathy of diabetes mellitus, since the prevalence of diabetes in our study was 31% and diabetes was not always present in asymptomatic patients. Nor can it be explained by the prevalence of silent single-vessel coronary lesions, which accounted for less than 50% of cases in our study, or low activity level in uremic patients, as some of these silent lesions were observed in participants with good functional capacity on ergometric testing. In short, this "clinical silence" might suggest some degree of uremic neuropathy that masks ischemic symptoms.

The utility of the ischemia detection tests to screen for coronary heart disease in patients in our series is highly controversial (*Table 3*). Given the high prevalence of cardiovascular disease in patients with ACKD and minimal symptoms, values of sensitivity and specificity close to 80% are necessary for reasonable and safe screening. In our case, these tests were not very useful to rule out significant coronary disease, as they had very low sensitivity and therefore resulted in false negatives that were subsequently confirmed with catheterization[25].

The burden of traditional cardiovascular risk factors was high in all our patients, with little variation, and there was no specific correlation with the presence of coronary lesions. This similarity in the number and type of risk factors limits their utility in stratifying the pretest probability of coronary disease in each patient. Therefore, it is necessary to identify emerging factors that predict individual risk in a high-risk population. Various epidemiological studies[26] point to lipoprotein A, hyperhomocysteinemia, and other factors inherent to uremia, such as inflammation, oxidative stress, anemia, alterations in calcium/phosphorus metabolism, dialysis fluids, and immunosuppressants, among others. Our study identified predictors that have statistically significant associations with significant coronary lesions, which would allow for identification of patients in a "very high cardiovascular risk" category (*Table 7*). The strongest predictors were the coronary calcification (HR 18.2, CI 95% 6.3-34.3, p <0.001), diabetes (HR 3.8, CI 95% 2.8-19.2, p 0.003) and cerebrovascular disease (HR 1.8, CI 95% 1.1-12.3, p 0.045). Given the atypical symptomatology of our patients and the low sensitivity of the ischemia tests, our experience suggests that the presence of these predictors should be an indication for coronary angiography, even in the absence of symptoms and with negative ischemia tests. Lupus can also be considered as a predictor, since it is associated with a similar prevalence of significant coronary lesions even in the absence of other traditional cardiovascular risk factors.

Table 7: Predictors associated with the presence of significant coronary lesions

Predictores	HR	CI 95%	P
Diabetes	3.8	2.8-19.2	0.003
Cerebrovascular disease	1.8	1.1-12.3	0.045
Coronary calcification	18.2	6.3-34.3	<0.001

There is not enough evidence in the general population to guarantee that preventive revascularization of asymptomatic individuals increases survival[27]. However, there is also no evidence that the lack of benefit can be extrapolated to patients with ACKD (stages 4-5), those at high cardiovascular risk, or candidates for kidney transplantation with a high rate of cardiovascular mortality. The data from the Andalusian Registry of Chronic Kidney Disease "SICATA 2010-2011" that served as a reference in the analysis of mortality show that cardiovascular disease is the first cause of death for patients on any renal replacement therapy. In a British registry, the reported cardiovascular mortality of transplant patients was 16%[28,29], while in the *US Renal Data System,* it was 30%[29]. In general, our results are very different from these figures, as our population had lower cardiovascular mortality overall (4.8%) and specifically in transplant patients (2.1%) (*Table 6*). These data can be applied to other groups in which invasive ischemic heart disease screening was performed[13], with cardiovascular mortality of 3.3%. Whereas Kumar et al. reported 1.9% mortality in transplant patients who underwent revascularization, our group did not document any cardiovascular death in this population during follow-up.

Finally, and to highlight the safety of coronary intervention in the overall study population, regardless of kidney transplantation, of the 83 procedures that were carried out (4 surgically and 79 percutaneously), we observed only one subacute stent thrombosis in the first month and 5 late clinical restenosis in dialysis patients, which resolved favorably. Therefore, given the technical advances in revascularization, the availability of new-generation *stents* and dual anti-platelet treatments and the ability to modulate risk factors during follow-up, coronary intervention seems to be beneficial in patients with ACKD.

Conclusions

In conclusion, the exclusion of patients with severe cardiac pathology (*Table 5*) and the use of medical and invasive coronary interventions contribute to the reduction of cardiovascular mortality in transplant patients. As a result of these interventions, as of 2015, cardiovascular disease was no longer the primary cause of death in transplant patients or in patients undergoing renal replacement therapy in our hospital. The main limitation of our study

is that it is observational at a single center, such that direct comparison with another group is not possible. However, the results obtained are similar (and in some respects superior) to those of other studies in which invasive screening for ischemic heart disease was performed in pretransplant patients, and cardiovascular mortality was reduced without increasing the number of complications inherent to angiographic studies. Nevertheless is necessary follow-up studies and the clinical daily life to confirm these results.

References

1. Couser WG, Remuzzi G, Mendis S, et al. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney International. 2011; 80(12): 1258-70.
2. Coresh J, Byrd-Holt D, Astor BC, et al. Chronic Kidney Disease Awareness, Prevalence, and Trends among U.S. Adults, 1999 to 2000. Journal of the American Society of Nephrology. 2005; 16(1): 180-8.
3. Hallan SI, Coresh J, Astor BC, et al. International Comparison of the Relationship of Chronic Kidney Disease Prevalence and ESRD Risk. Journal of the American Society of Nephrology. 2006; 17(8): 2275-84.
4. Otero González A, de Francisco ALM, Gayoso P, et al. Obesidad y funcion renal .datos del estudio epidemiologico: Prevalencia de la enfermedad renal cronica en España. Estudio EPIRCE. Nefrología. 2018; 38(1): 107-8.
5. Perico N, Remuzzi G. Chronic kidney disease: a research and public health priority. Nephrology Dialysis Transplantation. 2012; 27(suppl_3): iii19-iii26.
6. Hoerger TJ, Simpson SA, Yarnoff BO, et al. The Future Burden of CKD in the United States: A Simulation Model for the CDC CKD Initiative. American Journal of Kidney Diseases. 2015; 65(3): 403-11.
7. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: Systematic review. BMC Public Health. 2008; 8(1): 117.
8. Fried LF, Katz R, Sarnak MJ, et al. Kidney Function as a Predictor of Noncardiovascular Mortality. Journal of the American Society of Nephrology. 2005; 16(12): 3728-35.
9. Daar AS, Singer PA, Leah Persad D, et al. Grand challenges in chronic non-communicable diseases. Nature. 2007; 450: 494.
10. Go AS, Chertow GM, Fan D, et al. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. New England Journal of Medicine. 2004; 351(13): 1296-305.
11. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Archives of Internal Medicine. 2004; 164(6): 659-63.
12. Patel RK, Mark PB, Johnston N, et al. Prognostic Value of Cardiovascular Screening in Potential Renal Transplant Recipients: A Single-Center Prospective Observational Study. American Journal of Transplantation. 2008; 8(8): 1673-83.
13. Kumar N, Baker CSR, Chan K, et al. Cardiac Survival after Pre-emptive Coronary Angiography in Transplant Patients and Those Awaiting Transplantation. Clinical Journal of the American Society of Nephrology. 2011; 6(8): 1912-9.
14. Pilmore H. Cardiac Assessment for Renal Transplantation. American Journal of Transplantation. 2006; 6(4): 659-65.
15. Gibbons RJ, Balady GJ, Timothy Bricker J, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: A report of the American college of cardiology/American heart association task force on practice guidelines (committee to update the 1997 exercise testing guidelines) 11The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur.22This document was approved by the American College of Cardiology Foundation Board of Trustees in July 2002 and by the American Heart Association Science Advisory and Coordinating Committee in June 2002. When citing this document, the American College of Cardiology Foundation and the American Heart Association would appreciate the following citation format: Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40:1531–40.33Copies: This document is available on the World Wide Web sites of the ACC (www.acc.org) and the AHA (www.americanheart.org). A single copy of the complete guidelines is available by calling 800-253-4636 (US only) or writing the American College of Cardiology, Resource Center, 9111 Old Georgetown Road, Bethesda, MD 20814-1699. Ask for reprint No. 71-0231. To obtain a copy of the Executive Summary published in the October 1, 2002 issue of Circulation, ask for reprint No. 71-0232. To purchase additional reprints (specify version and reprint number): up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4426, fax 410-528-4264, or e-mail kbradle@lww.com.44(J Am Coll Cardiol 2002;40:1531–40.)55©2002 by the American College of Cardiology Foundation and the American Heart Association, Inc. Journal of the American College of Cardiology. 2002; 40(8): 1531-40.
16. Verberne HJ, Acampa W, Anagnostopoulos C, et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. European Journal of Nuclear Medicine and Molecular Imaging. 2015; 42(12): 1929-40.
17. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society,

Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2014; 63(4): 380-406.

18. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularizationThe Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European Heart Journal. 2014; 35(37): 2541-619.
19. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Atherosclerosis. 2016; 253: 281-344.
20. Authors/Task Force M, Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASDThe Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). European Heart Journal. 2013; 34(39): 3035-87.
21. Authors/Task Force M, Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertensionThe Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European Heart Journal. 2013; 34(28): 2159-219.
22. Kern MJ, Samady H. Current Concepts of Integrated Coronary Physiology in the Catheterization Laboratory. Journal of the American College of Cardiology. 2010; 55(3): 173-85.
23. Ohtake T, Kobayashi S, Moriya H, et al. High Prevalence of Occult Coronary Artery Stenosis in Patients with Chronic Kidney Disease at the Initiation of Renal Replacement Therapy: An Angiographic Examination. Journal of the American Society of Nephrology. 2005; 16(4): 1141-8.
24. Kumar N, Dahri L, Brown W, et al. Effect of Elective Coronary Angiography on Glomerular Filtration Rate in Patients with Advanced Chronic Kidney Disease. Clinical Journal of the American Society of Nephrology. 2009; 4(12): 1907-13.
25. Preston E, Adamson D, Frankel A, et al. Coronary assessment pre-renal transplantation in asymptomatic patients. J Am Soc Nephrol. 2006; 17: 171.
26. Bardají A, Martínez-Vea A. Enfermedad renal crónica y corazón. Un continuo evolutivo. Revista Española de Cardiología. 2008; 61(Supl. 2): 41-51.
27. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. New England Journal of Medicine. 2004; 351(27): 2795-804.
28. Ansell D, Tomson CR. UK renal registry 11th annual report (december 2008): chapter 15 the UK renal registry, UKRR database, validation and methodology. Nephron Clinical Practice. 2009; 111(Suppl. 1): c277-c85.
29. Ferguson RE. Predictors of end-stage renal disease: Boston University; 2012.