ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2015 January 26; 7(1): 1-46

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

A peer-reviewed, online, open-access journal of Cardiology

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World Journal of Cardiology

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Monthly Volume 7 Number 1 January 26, 2015

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

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PUBLICATION DATE
January 26, 2015

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World J Cardiol 2015 January 26; 7(1): 1-5
ISSN 1949-8462 (online)
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EDITORIAL

Opportunities and challenges of clinical trials in cardiology using composite primary endpoints

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Author contributions: All authors contributed to this manuscript.
Conflict-of-interest: The authors declare no conflicts of interest regarding this manuscript.
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Received: October 27, 2014
Peer-review started: October 27, 2014
First decision: November 27, 2014
Revised: December 19, 2014
Accepted: December 29, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

In clinical trials, the primary efficacy endpoint often corresponds to a so-called "composite endpoint". Composite endpoints combine several events of interest within a single outcome variable. Thereby it is intended to enlarge the expected effect size and thereby increase the power of the study. However, composite endpoints also come along with serious challenges and problems. On the one hand, composite endpoints may lead to difficulties during the planning phase of a trial with respect to the sample size calculation, as the expected clinical effect of an intervention on the composite endpoint depends on the effects on its single components and their correlations. This may lead to wrong assumptions on the sample size needed. Too optimistic assumptions on the expected effect may lead to an underpowered of the trial, whereas a too conservatively estimated effect results in an unnecessarily high sample size. On the other hand, the interpretation of composite endpoints may be difficult, as the observed effect of the composite does not necessarily reflect the effects of the single components. Therefore the demonstration of the clinical efficacy of a new intervention by exclusively evaluating the composite endpoint may be misleading. The present paper summarizes results and recommendations of the latest research addressing the above mentioned problems in the planning, analysis and interpretation of clinical trials with composite endpoints, thereby providing a practical guidance for users.

Key words: Composite endpoint; Competing risks; Multiple testing; Time-to-event; Adaptive designs

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Core tip: When planning a clinical trial with a composite primary endpoint: (1) Be aware of planning uncertainties when calculating the sample size and incorporate them in an adequate way; (2) Include a multiple testing strategy for an improved interpretation of the study results; (3) Take into account competing risks when analyzing the individual components of a composite endpoint; and (4) Analyze subsequent events in an adequate multi-stage model.

Rauch G, Rauch B, Schüler S, Kieser M. Opportunities and challenges of clinical trials in cardiology using composite primary endpoints. *World J Cardiol* 2015; 7(1): 1-5 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/1.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.1

RATIONALE FOR USING COMPOSITE ENDPOINTS

Clinical trials often focus on event variables as primary efficacy endpoints. In cardiology, "death" is often considered as the outcome of primary interest. However, clinically most relevant event types like "death" may be rare in many clinical conditions under investigation[1]. For example, due to the beneficial effects of modern treatments, patients with cardiovascular events like acute myocardial infarction experience a low mortality in the following years. Therefore, the assessment of differences in the survival curves of several treatment options may be difficult[2]. Using a rare event as primary endpoint results in the need of large sample sizes, a prolonged follow-up, and consequently an increased financial support, which often is not available. Thus, a "relevant and important treatment benefit" as claimed by the ICH E9 Guideline[3] cannot always be achieved by evaluating a single event endpoint, especially if this event type occurs with a low frequency[4]. By combining several types of events in a composite endpoint, the number of expected events is increased thereby intending an enlarged overall treatment effect. In the field of cardiovascular research, apart from death, clinical events like "non-fatal myocardial infarction", "non-fatal stroke", or "cardiovascular hospital admissions" also are of clinical interest and thus included into composite endpoints.

Most often, the composite endpoint is defined as a time-to-first-event variable, where different event types are counted as target events. In some applications, where the time period until the occurrence of an event is not of interest, composite endpoints can also be defined as binary event variables.

In summary, by using composite endpoints the required sample size is usually reduced and the study duration is shortened. Thereby, the use of composite endpoints very often is the only way to realize clinical trials investigating special interventions of interest.

Another important reason to use composite endpoints is when the effect of a new intervention may only be adequately assessed by considering several event variables. For example, atherosclerosis may result in a variety of clinical complications, and a single event endpoint therefore might not be sufficient for an adequate clinical evaluation[5]. Instead of formulating a multiple testing problem for several primary event endpoints, which always results in a loss of power, the ICH E9 Guideline[3] states that a composite outcome "addresses the multiplicity problem without requiring adjustment to the type I error".

CHALLENGES OF USING COMPOSITE ENDPOINTS

Planning and interpreting clinical trials with composite endpoints

Apart from the advantages of composite endpoints as outlined above, there also exist some serious problems and challenges.

In the planning stage of a clinical trial with a composite primary endpoint, calculation of the power may be particularly difficult as the assumed effect of the intervention depends on the effect sizes of the single components and their correlations. However, the level of evidence for these quantities may be low in many applications, as good historical data do not always exist. This complicates the choice of valid parameter assumptions in the planning phase of a study.

Analyzing and interpreting clinical trials with composite endpoints can be challenging as the composite effect as a "net measure" does not necessarily reflect the influence of the new intervention on the individual components[6,7]. Even in case a statistically significant and clinically relevant effect in the composite endpoint is observed, it may happen that the effects for some components are of very different magnitude or even point in opposite directions. As the efficacy of a treatment is usually judged on the composite effect alone, these situations may result in serious misinterpretations. This especially is a problem in case the composite endpoint consists of components of different clinical relevance and the less relevant endpoints refer to the larger effect sizes. The CPMP Guideline "Points to Consider on Multiplicity Issues"[8] therefore recommends to combine only components, which are expected to show effects of similar magnitude and with the same direction. This recommendation, however, may not be realistic in clinical practice. Even in thoroughly planned clinical studies, the initial assumptions about the underlying effect sizes can be wrong. Furthermore, the choice of the components must primarily be guided by their clinical relevance, and similar effects for all relevant event types cannot be expected in many cases.

Competing risks as a source of bias

The individual components of a composite endpoint usually define competing risks. In the presence of competing risks, the event rate of a specific event type also depends on the rates of all competing events[9]. For this reason, the event rates cannot be interpreted without simultaneously reporting all competing event rates. To illustrate this concept, assume that a novel therapeutic intervention in patients with cardiovascular disease is associated with a "one year mortality" of 0.3 as compared to 0.5 in the control group. Within the same group of patients, the rate for a "non-fatal myocardial infarction" might be 0.4 in the treatment group but only 0.2 in the control. If the death rates would not have been reported, one might come to the wrong conclusion that the control is superior to the treatment group with respect to "non-fatal myocardial infarction". When looking at the death rates, however, it becomes evident that the lower rate of "non-fatal myocardial infarction" in the control could exclusively be due to the fact that many patients had died before experiencing a (non-fatal) myocardial infarction. Ignoring the competing event scenario therefore may lead to a serious misinterpretation of treatment efficacy.

Therefore, methods taking into account competing events must be applied whenever the components of a composite endpoint are separately analyzed[5,8].

Follow-up beyond the first event

Composite time-to-first-event variables only take into account the first occurring event. This of course does not imply that there are no other subsequent events of interest occurring later. However, in the time to first event analysis these later events are not investigated, thereby leading to a loss of information.

On the other hand, an adequate and meaningful analysis of subsequent events may be a complex and difficult task, as-once a primary event has occurred the risk for all following events usually changes. For the latter reason models only focusing on a certain type of event, but not taking into account whether other events have occurred before, will yield biased results.

An unbiased approach to evaluate subsequent events would be to use more complex multistate models, which investigate all transition hazards between different subsequent event types[9]. The complexity of these models may be very high, and in order to get estimates with reasonable accuracy of all transition probabilities, the required sample size soon becomes unrealistically large. Therefore, for the confirmatory analysis of the composite and its components the time-to-first-event approach should usually be preferred. However, a descriptive presentation of the absolute numbers of all observed events should be provided in addition, keeping in mind that a correct interpretation of these results may be difficult.

NEW BIOMETRICAL METHODS FOR THE INTERPRETATION OF COMPOSITE ENDPOINTS

Overcoming uncertainties in sample size calculation

The standard approach to take account of planning uncertainties is the use of group-sequential or adaptive study designs. These designs allow stopping a trial at an interim stage due to an early demonstration of efficacy or due to futility. Whereas for group-sequential designs the number of interim analyses and the corresponding time points must be strictly planned in advance, adaptive designs additionally allow to change design parameters within an ongoing trial while still controlling the type I error rate.

A standard group-sequential design with one interim analysis (*e.g.*, after inclusion of 50% of the total study population) only offers two options-either to stop the study at interim or to continue the study until the full number of patients specified in the planning stage has been recruited[10-12].

In contrast, when using an adaptive design with one interim analysis, the sample size for the second stage can be recalculated based on the observed treatment effect at interim. If the observed effect at interim is large but not yet significant, only a small sample size for the second stage is needed, whereas the additionally required sample size is large, if the effect observed at interim is small. Moreover, it is possible to incorporate predefined stopping-for-futility rules in such designs, allowing to stop the study early with the acceptance of the null hypothesis whenever, on the basis of the interim data, the primary study goal becomes unrealistic. Thereby the number of patients being exposed to an ineffective treatment can be limited, and time and financial resources can be saved.

Another way to deal with uncertainties in the study planning assumptions is to use a more flexible power approach for sample size calculation. While the classical power is defined as the probability to reject the null hypothesis under a fixed parameter constellation of the alternative hypothesis, Rauch *et al*[13] proposed a so-called "expected power", which is defined as a weighted average over the classical power for different parameter constellations. Thereby, parameter constellations assumed to be more realistic in the planning stage of a study are assigned a higher weight, whereas other, less realistic assumptions are down-weighted. If there is no preexisting evidence available at all, equal weights for all possible parameter constellations might be assigned. The weights, which are defined by prior distributions, thus reflect the level of evidence or uncertainty in the planning stage. Calculating the sample size based on the "expected power" therefore defines a more robust approach in the common case of uncertain planning assumptions. The "expected power" can also be interpreted as a semi-Bayesian power approach[14].

Improving the interpretation of study results

The interpretation of study results may become difficult as the effect of the intervention under investigation on the composite endpoint does not necessarily reflect its effects on the single components. A possible solution of this problem would be to incorporate the (most important) components within the confirmatory test strategy by a multiple testing problem. However, this approach might seem to be contradictory as one main rationale for the use of a composite endpoint was to avoid multiplicity. A multiple testing problem always comes along with a certain loss in power resulting in an increase in sample size. The aim therefore is to create an adequate compromise by a multiple testing procedure, which mainly focuses on the composite endpoint but additionally gives some confirmatory evidence (at least) on the most important components.

In the literature, there exist a variety of either simple but also of more sophisticated multiple testing procedures, which can be applied to evaluate composite endpoints and their components. Simple applicable multiple testing strategies include the Bonferroni-Holm approach[15] or the sequential testing approach for hierarchically ordered hypotheses[16]. The application of at least a simple multiple testing strategy, which allow to address the components in a confirmatory way, is generally recommended. Even, if the trial is powered to

assess only the composite endpoint, these methods often allow a gain in information without increasing the sample size[17].

There also exist a variety of more sophisticated multiple testing procedures, which can be applied to provide sufficient power for the composite as well as for the (most relevant) components. So called "sequentially-rejective methods" represent extensions of the simple approaches outlined above. The underlying idea is to use an optimal splitting of the global significance level to test the individual hypotheses corresponding to the composite and the components. By "recovering" local levels of rejected hypotheses, the power loss due to multiplicity can be limited. Moreover, the test hypotheses for the components may be formulated less strictly than for the composite. For example, if the treatment under investigation already exhibits a significant and relevant effect on the composite, it might be sufficient to demonstrate in addition that the most relevant component is not adversely affected.

The application of sequentially-rejective multiple testing strategies in the evaluation of composite endpoints and their components has to be combined with the methodology for competing risks in order to provide an unbiased analysis and to prevent misinterpretations[18,19].

These methods can be further improved, if the correlation between the test statistics is taken into account. As an event referring to a single component always corresponds to an event in the composite endpoint, the test statistic of the composite and its components are usually highly correlated. By incorporating the information of the underlying correlation, the local significance levels of a multiple testing problem can be chosen less stringent, and the power loss often can be markedly decreased. These two approaches have been investigated recently by Rauch *et al*[20,21].

A completely different approach to improve the interpretation of clinical trials with composite endpoints is to use a weighted combined effect measure, which assigns higher weights to the more important components with the intention that an opposite effect in a relevant component (*e.g.*, "death") is less likely to be masked by a large effect in a component of secondary importance (*e.g.*, "cardiovascular hospital admission"). Recently, Pocock *et al*[22] and Buyse[23] proposed two similar combined effect measures, referred as the "win ratio" and the "proportion in favor of treatment", respectively. Both approaches are based on the same idea: All components are ordered with respect to their clinical relevance. The individual patients are compared between the groups. Based on the component of primary importance, for each comparison the patient with the "better" outcome is determined. In case no unique "winner" can be determined with respect to the most relevant component (*e.g.*, due to censoring, missing values or due to equal performance of both patients), the comparison will be based on the component of secondary importance and so on. This approach intends a higher weighting of the more relevant components, but also allows incorporating subsequent events.

Although this approach appears to be attractive in general, it also has some deficiencies. On the one hand, it can be shown that the weights, which are assigned to the single components, depend on the follow-up and the censoring distribution[24]. Moreover the weights are not standardized, that means they do not sum up to 1. As a consequence, the combined effect measure is not comparable between various studies as required-for example-within the context of meta-analyses. A small effect in the combined measure might thus be due to small effects in the components, but also could be explained by an unfavorable censoring distribution. Therefore, it cannot generally be deduced that these two approaches provide a gain in interpretation.

CONCLUSION

The use of a composite endpoint as primary efficacy variable can provide major advantages compared to a single event endpoint, if the event of primary interest is rare. However, care has to be taken when planning, analyzing and interpreting clinical trials with a composite endpoint as the primary efficacy outcome. The current statistical literature provides a variety of methods to overcome typical challenges arising from the use of composite endpoints thereby strengthening the interpretation of the results of clinical trials and avoiding serious misinterpretations. Now, the time has come to routinely incorporate these new methods into clinical trial applications.

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P- Reviewer: Amiya E, Iacoviello M, Teragawa H
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v7.i1.6

World J Cardiol 2015 January 26; 7(1): 6-9
ISSN 1949-8462 (online)
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Cardiac magnetic resonance in clinical cardiology

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Author contributions: Both authors contributed to this manuscript.
Conflict-of-interest: The authors report no conflicts of interest regarding the content herein.
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Received: October 27, 2014
Peer-review started: October 28, 2014
First decision: November 27, 2014
Revised: December 9, 2014
Accepted: December 29, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

Over the last decades, cardiac magnetic resonance (CMR) has transformed from a research tool to a widely used diagnostic method in clinical cardiology. This method can now make useful, unique contributions to the work-up of patients with ischemic and non-ischemic heart disease. Advantages of CMR, compared to other imaging methods, include very high resolution imaging with a spatial resolution up to 0.5 mm × 0.5 mm in plane, a large array of different imaging sequences to provide *in vivo* tissue characterization, and radiation-free imaging. The present manuscript highlights the relevance of CMR in the current clinical practice and new perspectives in cardiology.

Key words: Cardiac magnetic resonance; Gadolinium enhancement; Myocarditis; Myocardial; Cardiomyopathy

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Core tip: The present manuscript highlights the relevance of cardiac magnetic resonance in the current clinical practice and new perspectives in cardiology.

Kumar A, Bagur R. Cardiac magnetic resonance in clinical cardiology. *World J Cardiol* 2015; 7(1): 6-9 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/6.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.6

INTRODUCTION

Over the last decades, cardiac magnetic resonance (CMR) has transformed from a research tool to a widely used diagnostic method in clinical practice. While other imaging modalities like echocardiography and cardiac computed tomography depend solely on tissue density, the most important feature that CMR affords to the diagnostic toolset of the clinic cardiologist, is its ability to provide with a very-high spatial resolution, up to 0.5 mm × 0.5 mm in plane, a large array of different imaging sequences in order to assess *in-vivo* tissue characterization, in addition to radiation-free imaging. These imaging sequences investigate the presence of protons in different chemical environments, thereby allowing conclusions on the presence of fat, water (edema), blood or myocardium among other tissues. The addition of a contrast agent enhances the diagnostic capabilities to assess perfusion, fibrosis and necrosis as well as identify thrombus. Exploiting these different imaging sequences, in addition to the capability of performing high spatial resolution imaging in any desired imaging plane in 3-dimention (3D)

space, CMR provides what could be also called "*in-vivo* pathology". Therefore, this has led to substantial progress in the assessment of patients with ischemic and non-ischemic heart disease[1].

ISCHEMIC HEART DISEASE

Acute ischemic disease

After the development of electrocardiographic-triggered fast CMR imaging using gradient-echo sequences, the late gadolinium enhancement (LGE) imaging technique opened new horizons for CMR at the beginning of the century[2-4]. The method exploits the fact that gadolinium-based contrast agents have a much higher volume of distribution in necrotic and fibrotic tissue, when the cardiomyocytes have lost their cell wall integrity or have been replaced by collagen. Late enhancement imaging therefore allows for an assessment of viability with unprecedented image contrast and very-high spatial resolution. Clinical applications included the detection, when the diagnosis is unclear, the differences between acute myocardial infarction (AMI) and chronic ischemic cardiomyopathy[5,6]. The assessment of viability predicts functional recovery in acute myocardial infarction based on the transmural extent of the necrosis[7].

The use of CMR in this setting was subsequently enhanced by the development of water-sensitive T2-STIR sequences, allows the assessment of tissue edema. Of note, since only acute infarction has edema, the combination with LGE imaging, T2-STIR helps to differentiate acute from chronic myocardial infarction[6,8,9]. The edematous tissue in AMI is thought to reflect the area-at-risk, allowing for quantitative assessment of salvaged myocardium after reperfusion therapy[10-12]. This can be measured as the difference between edematous tissue minus necrotic tissue, where the latter is seen on LGE.

Microvascular obstruction (MVO) as a consequence of ischemia and reperfusion injury in AMI is reliably detected with first-pass perfusion imaging or the LGE sequence applied early after contrast injection. The presence of MVO is an independent predictor of adverse outcome, independent of infarct size and left ventricular systolic function[13,14]. Severe microvascular injury can be complicated by reperfusion hemorrhage, which again can be visualized and also quantified with a specific CMR sequence (T2*-weighted imaging)[15]. It is currently unclear whether hemorrhage has independent prognostic effects beyond MVO, since insufficient sample size and flaws in study design, limited most of the clinical studies trying to address this question.

Chronic ischemic disease

Newer imaging approaches are emerging to fine-tune risk assessment in chronic ischemic heart disease, and help, for example, with patient's selection for implantable cardioverter-defibrillators (ICD) implantation. Several authors have shown that the peri-infarct zone between chronic infarction tissue and healthy myocardium displays an intermediate contrast signal. The extent of this "grey-zone" has been associated with ventricular arrhythmia and major adverse cardiac events, probably due to electrical re-entry circuits being located in this area[16]. Prospective studies are under way to assess, whether advanced tissue characteristics such as the LGE grey-zone would be helpful to better select patients for ICD implantation, thereby switching selection criteria from the current left ventricular systolic function to a tissue characteristic. Hence, an improved patient's selection could be of tremendous help, allowing for better selection of patients at higher risk, and also avoiding potentially unnecessary ICD implantations.

In stable coronary artery disease, CMR perfusion imaging with and without stress agents (predominantly adenosine) can detect myocardial ischemia with high accuracy. Depending on the reference standard, it has been reported a sensitivity and specificity of about 90% and 70%-90%, respectively, for the detection of myocardial ischemia[17,18]. Advantages of CMR in this setting include a higher spatial resolution than nuclear imaging methods, allowing the diagnosis of sub-endocardial perfusion defects and microvascular disease[19]. Research efforts are under way to detect ischemia without using contrast agents. Indeed, blood-oxygen-level-dependent (BOLD) sequences are able to create image contrast-based on the tissue's oxygen content in the brain, and initial reports have suggested that modified BOLD sequences could also be applied in the heart[20,21]. This approach, once developed to a clinically applicable tool, promises to revolutionize the ischemia detection field by measuring myocardial oxygen directly, and moving away from perfusion as a surrogate marker.

NON-ISCHEMIC HEART DISEASE

Cardiac magnetic resonance has allowed significant progress in understanding of non-ischemic cardiomyopathies. Beyond accurate assessment of ventricular volume and function, tissue characterization using T1, T2, T2*, perfusion and contrast-enhanced sequences allows for comprehensive tissue characterization as a non-invasive pathology[22-24]. This further contributes to identify the etiology of heart failure, and initial studies have started to identify CMR-based tissue characteristics as prognostic markers[25-28]. In fact, CMR is now the reference diagnostic tool to diagnose myocarditis, as recommended by the Lake Louise consensus criteria[29]. Importantly, T2-weighted imaging identifies edema as a marker of inflammation in acute/active disease, and late gadolinium enhancement is typically present in a "patchy", thus, a non-ischemic pattern. Of note, the combined imaging sequences yield a diagnostic power to assess myocarditis with a sensitivity of 76% and specificity of 96%[30]. Noteworthy, patients with LGE in myocarditis have a worse prognosis than patients

without LGE[31]. Moreover, infiltrative cardiomyopathies such as amyloidosis are reliably diagnosed based on their typical pattern of signal change on T2 and LGE, usually involving the entire myocardium as an organ[32]. The diagnostic power of CMR is especially well exploited in iron deposition disease like thalassemia and hemochromatosis. In fact, CMR can semi-quantitatively assess iron deposition by measuring the T2* value of myocardium. The latter highly correlates with myocardial iron content[33,34]. Furthermore, it is of prognostic value as can be used to monitor the effect of iron chelation therapy, let's say, to start, titrate or finish iron chelation therapy.

THE FUTURE OF CMR

Cardiac magnetic resonance is still a relatively "young" imaging technique, and new technical developments are continuously entering the clinical arena. While current imaging sequences mostly provide a contrast suited for visual analysis, imaging methods that quantitatively map T1, T2 and T2* characteristics are under evaluation[35]. Moving away from qualitative assessment to semi-quantitative or quantitative image analysis will allow increased diagnostic accuracy and reduced observer bias, as well as improve inter-study variability. Normal values will have to be established for different field strengths, and differences in sequence programming between different CMR vendors as a source of variability of normal values will have to be addressed. Eventually, advanced tissue characterization with mapping sequences could reduce (but probably not eliminate) the dependence on gadolinium-based contrast agent. New imaging sequences that apply self-triggering may eliminate the need for electrocardiographic tracing and breath-hold maneuvers[36], further increasing patient comfort and reduce scan time.

CONCLUSION

Cardiac magnetic resonance has become a basic diagnostic tool in cardiovascular medicine. The next decade will be marked by clinical trials investigating the prognostic value of the detailed imaging findings that can be obtained today, and may guide therapy and improve patient prognosis.

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P- Reviewer: Can M, Izawa KP, Kirali K **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v7.i1.10

World J Cardiol 2015 January 26; 7(1): 10-18
ISSN 1949-8462 (online)
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TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (2): Coronary artery disease

Coronary artery disease in women: From the yentl syndrome to contemporary treatment

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Author contributions: All authors have contributed equally to the development of this review.
Conflict-of-interest: All authors declare no conflict of interest.
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Received: January 27, 2014
Peer-review started: January 30, 2014
First decision: March 19, 2014
Revised: November 16, 2014
Accepted: December 3, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

In recent years attention has been raised to the fact of increased morbidity and mortality between women who suffer from coronary disease. The identification of the so called Yentl Syndrome has emerged the deeper investigation of the true incidence of coronary disease in women and its outcomes. In this review an effort has been undertaken to understand the interaction of coronary disease and female gender after the implementation of newer therapeutic interventional and pharmaceutics' approaches of the modern era.

Key words: Yentl syndrome; Women coronary disease; Acute coronary syndromes; Female gender; Invasive treatment

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Core tip: Coronary disease although remains a leading cause of morbidity and mortality in women, is however underestimated mainly because of the protective role of estrogens that results in lower rates of the disease until the age of mid-fifty. In this review detailed information about the prevalence and the consequences of the disease in women are quoted as well as evidence concerning the results of invasive treatment and use of modern drug therapy.

Vaina S, Milkas A, Crysohoou C, Stefanadis C. Coronary artery disease in women: From the yentl syndrome to contemporary treatment. *World J Cardiol* 2015; 7(1): 10-18 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/10.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.10

INTRODUCTION

Coronary artery disease (CAD) constitutes a form of modern epidemic, as it still remains the leading cause of mortality and morbidity in the ageing western societies[1]. The prevalence of CAD in the general population varies, depending on age and sex. In terms of age, there is a trend of more incidents in older ages. Concerning sex, until the age of 60 years old, the predicted probability of having an acute myocardial infarction (AMI) is by

Table 1 Remaining lifetime risks for cardiovascular disease and other diseases among men and women free of disease at 40 and 70 years of age remaining life[57]

Diseases	Remaining lifetime risk at the age of 40 yr		Remaining lifetime risk at the age of 70 yr	
	Men	Women	Men	Women
Any CVD	2 in 3[1]	1 in 2[1]	2 in 3[2]	1 in 2
CHD	1 in 2	1 in 3	1 in 3	1 in 4
AF	1 in 4	1 in 4	1 in 4	1 in 4
CHF	1 in 5	1 in 5	1 in 5	1 in 5
Stroke	1 in 6[3]	1 in 5[3]	1 in 6	1 in 5
Dementia	…	…	1 in 7	1 in 5
Hip fracture	1 in 20	1 in 6	…	…
Breast cancer	…	1 in 8	…	1 in 15
Prostate cancer	1 in 6	…	1 in 9	…
Lung cancer	1 in 13	1 in 16	1 in 15	1 in 20
Colon cancer	1 in 19	1 in 21	1 in 25	1 in 27
DM	1 in 3	1 in 3	1 in 9	1 in 7
Hypertension	9 in 10[3]	9 in 10[3]	9 in 10	9 in 10
Obesity	1 in 3	1 in 3	…	…

[1]Age 45 yr; [2]Age 65 yr; [3]Age 55 yr. AF: Atrial fibrillation; CHD: Coronary heart disease; CHF: Congestive heart failure; CVD: Cardiovascular disease; DM: Diabetes mellitus; …: Not estimated.

far higher in men than in women (60.6% *vs* 33.0%, respectively)[1]. Therefore, CAD is widely believed to be a man's disease, although it accounts for more deaths in women at the age of 35 years than breast cancer (Table 1)[2]. This has been mainly attributed to the protective role of estrogens in the cardiovascular system as they enhance vascular function, reduce the inflammatory response, increase metabolism and insulin sensitivity and finally promote cardiac myocyte and stem cell survival[3]. As a consequence, female hormones may partially account for women's longevity observed in randomized control trials, where women with CAD are older than men and have more co-morbidities such as diabetes, hypertension and chronic kidney disease[4,5]. At menopause, the lack of the protective effect of estrogens leads to a 10-fold increase in the prevalence of CAD in women compared to a 4.6 fold increase in men of the same age[6]. Finally, by the 7th decade of life the increasing rate of CAD among women results in similar rates of the disease among the two genders, although lifestyle factors seem to have a different impact on clinical outcome between gender[1,7,8].

Due to the above mentioned characteristics of the female gender, and the fact that the majority of trials more often enroll younger patients, the representation of women in clinical trials was until recently relatively low, approximately 30% (Table 2)[9,10]. Even in one of the largest contemporary trials designed to compare outcomes between invasive and conservative pharmacological treatment in patients with stable CAD, the COURAGE trial (Clinical Outcomes Utilizing Revascularization and AGgressive Drug Evaluation), men encountered for approximately 85% of the study group[11]. As a result, women suffering from CAD are handled diagnostically and therapeutically based on conclusions drawn mainly from male populations. This observation underscores the need for a more gender focused approach both in every day clinical practice but also in large scale trials. The purpose of the present review is to explore the available data depicting the best strategies to recognise and treat CAD in women.

WOMEN AND SYMPTOM PRESENTATION

It has been demonstrated that women tend to present for chest pain evaluation in the emergency room at a greater rate compared to men (4.0 million visits for women *vs* 2.4 million visits for men). However, women tend to present with less typical symptoms, such as fatigue (70.7%), sleep disturbance (47.8%) and shortness of breath (42.1%)[12], back pain, indigestion, weakness, nausea/vomiting, dyspnoea and weakness[13,14]. At an older age, with more co-morbidities including diabetes, peripheral vascular disease, chronic kidney disease and hypertension[15]. A great amount of literature explored this phenomenon giving rise to large scale clinical trials which resulted in the identification of three paradoxes with regard to female sex and CAD manifestation[13]. (1) Women have disproportionately lower burden of atherosclerosis and obstructive CAD compared with the extent of angina they complain for; (2) Compared to men, women have less severe CAD despite the fact that they are older with a greater risk factor burden; and (3) Even though CAD is less evident in women, as illustrated by invasive diagnostic imaging modalities, females still have a more adverse prognosis compared to men.

Another parameter of great importance is the increasing prevalence of the cardiac X syndrome or coronary microvascular dysfunction among women of post-menopausal age. It is evident that almost 40% of the operated coronary angiographies reveal non obstructive atherosclerosis although patients present with anginal symptoms and positive exercise training results[16]. A large proportion out of 30% of these findings is attributed to coronary microvascular dysfunction as no other identifiable

Table 2 Women are considerably underrepresented in clinical trials[9]

Study	Sample MT.PCI	Enrollment *n*	Mean age (yr)	Male (%)	DM (%)	% Prior MI	1/2/3-Vessel CAD	% No symptoms	% Mean EF	% Follow up, yr
RITA-2	514/504	1992-1996	58 (Median)	82	9	47	60/33/7	20	ND[1]	7
ACME-1	115/112	1987-1990	60	100	18	31	100/0/0	9	68	2.4-5[2]
ACME-2	50/51	1987-1990	60	100	18	41	0/100/0	18	67	2.4-5[2]
AVERT	164/177	1995-1996	59	84	16	42	56/44/0	16	61	1.5
Dakik *et al*[58]	22/19	1995-1996	53	59	ND	100	44/41/15	0	46	1
MASS	72/72	1988-1991	56	58	18	0	100/0/0	0	76	5
MASS II	203/205	1995-2000	60	68	30	41	0/42/58	ND	67	1
ALKK	151/149	1994-1997	58	87	16	100	100/0/0	0	ND[3]	4.7
Sievers *et al*[59]	44/44	ND	56	ND	0	55	100/0/0	ND	ND	2
Hambrecht *et al*[60]	51/50	1997-2001	61	100	23	46	58/27/15	0	63	1
Bech *et al*[61]	91/90	ND	61	64	12	25	66/28/6	0	65	2

[1]Ninety-three percent of patients had very good or excellent wall motion score; [2]Ninety-seven percent of patients were in New York Heart Association class 1; [3]Follow-up was 2.4 years (mean) to follow-up interview, 3 years (mean) to follow-up exercise test, and 5 years (median) for ascertainment of deaths and MI events. MT: Medical treatment; DM: Diabetes mellitus; EF: Ejection fraction; ND: No data available.

cause can be found. The most interesting aspect of this group of patients is the fact that it is consisted in its great proportion (almost 70%) of post-menopausal women[17]. In contrast to the findings of earlier studies that microvascular angina does not affect long term prognosis[18], it is evident nowadays from a large retrospective analysis of 11223 patients referred for coronary angiography with stable angina, that patients with non-obstructive CAD consolidate a further increase in the risk of coronary events and of all-cause mortality (HR = 1.85; 95%CI: 1.51-2.28; and 1.52; 95%CI: 1.24-1.88, respectively)[19].

Thus, women are frequently a clinical challenge for the cardiologist and their symptom misinterpretation may lead to the wrong diagnosis and treatment with potentially unfavourable consequences. Symptom evaluation and recognition in women is a matter of great importance, since it has been shown that when typical symptoms accompany an acute coronary syndrome (ACS) there is no difference in the disease diagnosis between women and men[20]. Moreover, when prodromal symptoms are recognised in women before an ACS, women have better survival in comparison to men[21].

WOMEN AND TREATMENT STRATEGIES

Not only diagnostic evaluation of women may be misleading, but also the appropriate treatment selection can be difficult. It was already recognized in 1991 that women suffering from CAD had less chances to be introduced either in coronary angiography or percutaneous coronary intervention (15.4% of women *vs* 27.3% of men, $P < 0.001$)[22]. This approach was demonstrated even in cases were admission symptoms were more prominent in women than in men[23]. Unlike men, women were submitted less frequently to any diagnostic or therapeutic intervention creating in this way dissimilarity on curing procedures. This alarming fact was described by Bernadine Healy, the first woman director of National Health Institute in United States, as the Yentl syndrome named after the Jewish heroine of Isaac Singer, who was masqueraded as a boy in order to be educated in the Talmud philosophy. Healy concluded that when a woman has been shown to have extensive CAD, like men, only then she gets the appropriate treatment[24]. Since, a plethora of studies examined gender differences in order to provide the best treatment options for women.

WOMEN AND PERCUTANEOUS CORONARY INTERVENTION

One of the first studies comparing the impact of percutaneous coronary interventions (PCI) with bare metal stent (BMS) implantation between females and males, revealed that women had 50% more chance of death in comparison to men after adjustment for age, co-morbidities, and extend of coronary atherosclerosis[25]. However, in the same analysis, after final adjustment for Body Surface Area, mortality rates were similar between the two genders, although a slighter increased rate of stroke, vascular complications and repeat in-hospital revascularization was observed in women[25]. Similar results were reported in a retrospective analysis from Mayo Clinic investigating 18885 consecutive, patients who underwent PCI between 1979 and 1995 (early group) and between 1996 and 2004 (late group)[26]. The results indicated no difference in terms of 30-d mortality, while after adjustment for baseline risk factors, again there was no difference observed in short or long term mortality between the two genders (Figures 1 and 2)[26]. The study indicated that between the two groups a decrease in 30 d mortality was observed in both genders during the 25-year follow up period.

A retrospective study from Rotterdam investigated the outcomes of Sirolimus Eluting Stents, Pacliataxel Eluting Stents and BMS in women[27]. In this study, even though women had worse baseline characteristics compared to men, no differences in 3-year outcomes were detected between males and females.

A recent meta-analysis, which included 43904 patients (26.3% women) in 26 trials, assessed the safety and

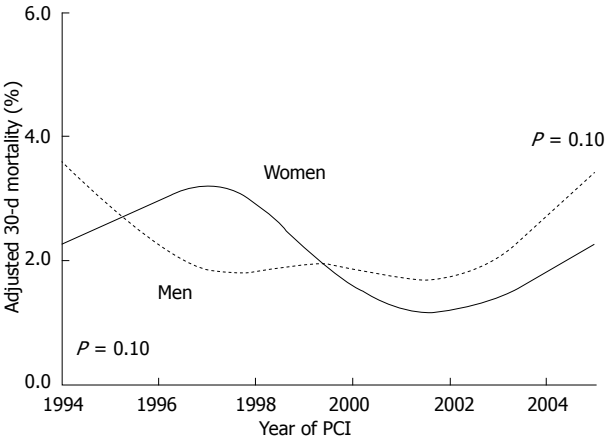

Figure 1 Mayo clinic percutaneous coronary interventions registry: 12798 pts adjusted 30-d mortality after percutaneous coronary interventions[26].

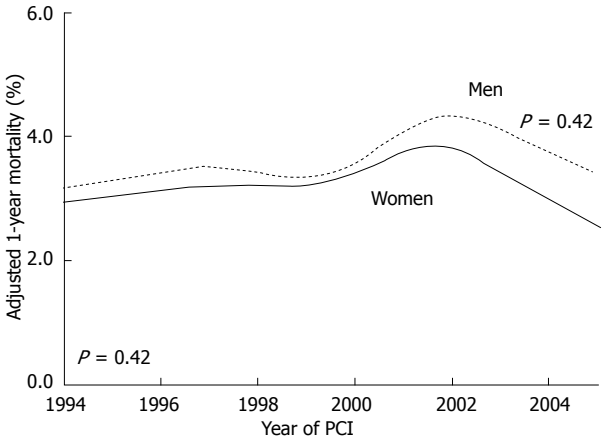

Figure 2 Mayo clinic percutaneous coronary interventions registry: 12798 pts Adjusted 1-year mortality after percutaneous coronary interventions[26].

efficacy of DES in women[28]. The study showed that DES implantation in women was more effective and safe than BMS implantation. Furthermore, it was observed that 2nd and 3rd generation DES, such as everolimus-eluting Xience and Promus stents, zotarolimus-eluting Endeavor and Resolute stents, biolimus-eluting Biomatrix and Nobori stents, and sirolimus-eluting Yukon stents, were associated with an improved safety profile compared with early-generation DES[28]. These results suggest that women undergoing PCI may benefit more when DES and moreover newer generation DES are used.

An interesting meta-analysis was designed in order to evaluate whether female gender is an independent risk factor for repeated coronary revascularization after PCI. The results indicated that although female sex increases the short term rate of repeated revascularization after PCI the long term rate was the same between the two genders clarifying the fact that even for this parameter female gender is not an independent risk factor[29].

Bleeding complications at the point of vascular puncture, hematomas and retroperitoneal bleedings are decreased in the current era. This is mainly due to introduction of less aggressive anticoagulant regimens, adjustment of heparin dose according to body mass index and smaller size catheters. However, women still continue to be at 1.5 to 4 times greater risk for bleeding in comparison to men (Table 3)[30]. Reduced Body Surface Area, altered pharmacokinetics and diminished drug metabolism are the main aspects of female gender that attribute mostly in these higher bleeding rates.

Newer anticoagulant agents were recently introduced in clinical practice raising expectations for further bleeding risk reduction. In order to evaluate this hypothesis, novel studies were contacted to evaluate the action of direct thrombin inhibitor bivalirudin (ANGIOX®) in both genders who suffered from moderate and high-risk ACS[31]. Out of 7789 patients submitted to PCI, 2561 received heparin and Ⅱb-Ⅲa glycoprotein inhibitor, 2609 received bivalirudin in combination to Ⅱb-Ⅲa glycoprotein inhibitor and 2619 received bivalirudin solely. The group of patient to receive bivalirudin in comparison to the group of patient receiving heparin in combination to Ⅱb-Ⅲa glycoprotein inhibitor displayed the same degree of ischemic events but with a lesser degree of major bleeding (4% *vs* 7%, $P < 0.0001$)[31]. Interestingly, bivalirudin alone decreased the variance of bleeding between the two genders, but it did not completely eliminate it.

In order to achieve decreased bleeding rates in women, the idea of radial approach during intervention was implemented into clinical practice. However, due to women's smaller vessel size and lower pain threshold it was revealed that 14% of women were finally switched to femoral approach in contrast to 1.7% of men[32]. In the same study however, during 299 radial interventions in women no major bleeding was observed, whereas in 601 femoral intervention, 25 major bleedings where recorded ($P = 0.0008$). In addition, radial approach was related with a lower rate of minor bleeding (6.4% *vs* 39.4% $P = 0.00001$). These favourable results indicate that radial approach during PCI in women is safer in terms of bleeding, even though there are more difficulties to initiate the procedure through the particular access site.

WOMEN AND CORONARY ARTERY BY-PASS GRAFTING

In the past, women submitted to CABG were shown to have higher perioperative morbidity and mortality compared to men[33-35]. These first results raised the issue of CABG safety in women and initiated the conduction of several newer trials. Indeed, over 20 trials investigated the impact of CABG in women compared to men. A recent meta-analysis confirmed that women experience higher mortality rates in comparison to men in terms of short-, mid- and long-term follow-up with the higher mortality recorded in the short-term period[36]. Several explanations for this observation have been proposed such as the delayed reference of women to CABG when

Table 3 Women have higher rate of vascular complications after percutaneous coronary interventions[30]

Study	*n*	Vascular complications		
		Women	Men	*P*-value
Alfonso	981	11/157 (7.0%)	16/824 (2.0%)	< 0.01
Antoniucci	1019	14/234 (6.0)	24/785 (3.0%)	0.01
BOAT	989	6/237 (2.5%)	6/752 (0.8%)	0.05
CAVEAT	512	14/128 (10.8%)	22/384 (5.8%)	0.003
NACI	2855	39/971 (4.0%)	28/1884 (1.5%)	< 0.05
NCN	109708	1955/36204 (5.4%)	1985/73504 (2.7%)	< 0.001
NHLBI	2136	24/555 (4.4%)	36/1581(2.3%)	< 0.05
NHLBI	2524	44/883 (5.0%)	43/1641(2.6%)	< 0.01
STARS	1965	44/570 (7.8%)	39/1395 (2.8%)	< 0.01
Trabatoni	1100	15/165 (9.3%)	33/935 (3.5%)	0.004
Welty	5989	34/2096 (1.6%)	23/3893 (0.6%)	< 0.001
WHC	7372	78/2064 (3.8%)	125/5308 (2.4%)	< 0.001
Combined	137150	2278/44264 (5.1%)	2380/92886 (2.6%)	

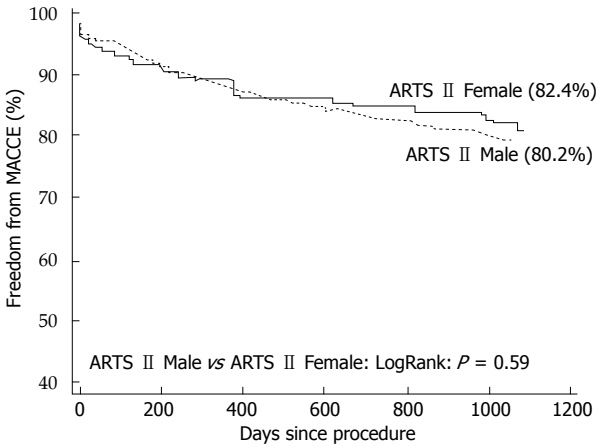

Figure 3 Freedom from major adverse cardiac and cerebrovascular events after percutaneous coronary intervention in Arterial Revascularization Therapies Study-Part Ⅱ[41].

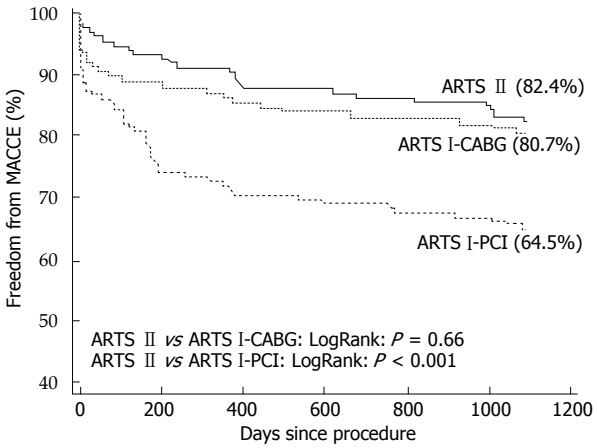

Figure 4 Freedom from major adverse cardiac and cerebrovascular events after coronary artery by-pass grafting and percutaneous coronary intervention with bare metal stent and sirolimus eluting stent implantation in women[41].

CAD extends to a greater degree, the smaller size of women coronary vessels that creates technical issues to the surgeon or finally the limited use of left internal mammary artery in women[37-39].

Arterial Revascularization Therapies Study Part I (ARTS I) was one of the first studies to compare CABG and PCI in women. The study demonstrated that for a total of 1205 patients there was no significant difference in terms of death, stroke, or myocardial infarction between the two genders. However, stenting was ascossiated to a greater need for repeated revascularization[40,41].

Newer studies in the Drug Eluting Stent (DES) era sought to further investigate the effect of gender on PCI and CABG outcomes. The multicenter randomized study Arterial Revascularization Therapies Study-Part Ⅱ (ARTS Ⅱ) was designed to evaluate the outcomes of Sirolimus Eluting Stent implantation in comparison to BMS implantation and Coronary Artery Bypass Grafting (CABG) in patients with multivessel CAD[41]. In ARTS Ⅱ, although women tended to have more risk factors compared to men, they experienced the same rate of adverse events with men at 30 d, one year and three years after Sirolimus Eluting Stent implantation (Figure 3)[37]. Additionally, it was observed that both genders had a more favorable clinical outcome with Sirolimus Eluting Stents compared with BMS but similar to CABG (Figure 4)[41].

These results could potentially institute PCI as the first choice treatment in women with multivessel disease.

WOMEN AND ACUTE CORONARY SYNDROMES

The vast majority of women, about 60%, experience an acute coronary syndrome (ACS) or sudden cardiac death as the first manifestation of the disease[42]. The initial results comparing gender differences in patients with ACS were presented in the pre-thrombolytic era, where a 28% mortality rate was demonstrated in women compared to a 16% mortality among men[43]. Women also experienced a 3 fold higher rate of reinfarction. In the following years, the introduction of thrombolysis decreased the total mortality rates in the general population. However,

a discrepancy was still evident between the two genders (30 d unadjusted mortality rate was 13.1% in women and 4.8% in men)[44]. Newer, large scale studies were undertaken in order to re-evaluate these results in the modern era of invasive approach to ACS. One of the largest trials investigating these aspects enrolled 78254 patients (39% women) with AMI in 420 United States hospitals from 2001 to 2006[45]. The results reconfirmed the data observed in previous trials. The study showed that women with ACS are older, with more comorbidities such as hypertension, diabetes, and metabolic syndrome and tend to present less often with ST-elevation AMI[46-48]. Adjusted analysis revealed no differences in terms of mortality between the two genders for ACS, but in the subgroup of ST Elevation Myocardial Infarction (STEMI) there was a statistically significant and almost double proportion of mortality in women (10.2% women *vs* 5.5% men, $P < 0.0001$). An important conclusion from this trial was the fact that women received less often aspirin and b-blockers and were less often treated in an invasive manner with percutaneous transluminal coronary angioplasty.

This approach was also noticed in an earlier contacted study in Minnesota (46% less chances of invasive approach) as well as in a in a Swiss national registry where the rate of women introduced in PCI was significantly lower than men (OR = 0.70; 95%CI: 0.64 to 0.76)[15,48].

These observations raised the question of whether physicians prefer more conservative strategies because women have higher mortality rates with invasive procedures or whether women are less willing to undergo such a procedure. PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis 1 and 2 studies evaluated 520 patients with STEMI treated with thrombolytics and 530 patients treated with primary PCI. Women treated with thrombolytics had almost two fold higher mortality than women treated with primary PCI ($P = 0.043$)[49]. Therefore, although patient demographic data were not adjusted to body mass index, which could have an effect on the unadjusted doses of streptokinase used, it can be concluded that primary PCI to treat women with AMI is superior to a more conservative approach. Similar results were demonstrated in the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries Ⅱ-B and in a sub-analysis of the Primary Angioplasty in Myocardial Infarction trial comparing newer thrombolytic agents *vs* PCI[50,51]. More recent studies showed that mortality and major adverse cardiac events, though higher among women with primary PCI in unadjusted analyses, are comparable in both genders after adjusting for age, hypertension, smoking, diabetes mellitus, stent diameter, and time between symptoms onset and ambulance arrival[52-55]. A meta-analysis that included 8 trials and almost 10115 patients, demonstrated that low-risk women with ACS may benefit from a more conservative approach. However, males and high-risk females with ACS treated with an invasive strategy have similar clinical outcome in terms of death, MI, or rehospitalisation for ACS[56].

CONCLUSION

It has been consistently shown that women who are suffering from CAD usually present with less typical symptoms, at an older ager and with more co-morbidities compared with men. Therefore, they constitute a high risk group that potentially poses a diagnostic and therapeutic challenge. However, it seems that in the modern era, where sophisticated interventional and surgical techniques have emerged, women significantly benefit from an early invasive approach provided an intense medical monitoring is implemented.

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World J Cardiol 2015 January 26; 7(1): 19-25
ISSN 1949-8462 (online)
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REVIEW

Helicobacter pylori: Does it add to risk of coronary artery disease

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Author contributions: Sharma V and Aggarwal A contributed to this paper.
Conflict-of-interest: No conflicts.
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Telephone: +91-98-11060025
Received: October 17, 2014
Peer-review started: October 20, 2014
First decision: November 27, 2014
Revised: December 14, 2014
Accepted: December 29, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

Helicobacter pylori (*H. pylori*) is a known pathogen implicated in genesis of gastritis, peptic ulcer disease, gastric carcinoma and gastric lymphoma. Beyond the stomach, the organism has also been implicated in the causation of immune thrombocytopenia and iron deficiency anemia. Although an area of active clinical research, the role of this gram negative organism in causation of atherosclerosis and coronary artery disease (CAD) remains enigmatic. CAD is a multifactorial disease which results from the atherosclerosis involving coronary arteries. The major risk factors include age, diabetes mellitus, smoking, hypertension and dyslipidemia. The risk of coronary artery disease is believed to increase with chronic inflammation. Various organisms like Chlamydia and Helicobacter have been suspected to have a role in genesis of atherosclerosis *via* causation of chronic inflammation. This paper focuses on available evidence to ascertain if the role of *H. pylori* in CAD causation has been proven beyond doubt and if eradication may reduce the risk of CAD or improve outcomes in these patients.

Key words: Extra gastric; Coronary artery disease; *Helicobacter pylori*; Atherosclerosis; Inflammation

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Core tip: Coronary artery disease (CAD) is a multifactorial disease and inflammation plays an important role in Atherogenesis. *Helicobacter pylori* (*H. pylori*) is speculated to be one organism which may incite the inflammatory response thereby predisposing infected individuals to CAD. This paper looks at clinical evidence in relation to *H. pylori* infection and CAD and also examines the evidence of effects of eradication of *H. pylori* on CAD and its risk factors.

Sharma V, Aggarwal A. *Helicobacter pylori*: Does it add to risk of coronary artery disease. *World J Cardiol* 2015; 7(1): 19-25 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/19.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.19

INTRODUCTION

Helicobacter pylori (H. pylori), first identified by Marshall and Warren in 1982, is a ubiquitous gram negative bacterium. A mixture of serendipity and diligent research lifted the veil off this enigmatic organism which was first

thought to be Campylobacter like. The Easter holidays of 1982 had ensured that the culture plates were not destroyed after 48 h of absence of growth and led on to the discovery of *H. pylori*[1]. However, it was after much perusal that the scientific community accepted the bacterium-ulcer-cancer dogma eventually culminating in the 2005 Nobel Prize[2]. Over years it has become clear that this bacterium is responsible for many disease other than the gastric diseases. In the stomach *H. pylori* is implicated in the causation of chronic gastritis, peptic ulcer (gastro-duodenal), gastric MALTOMA (mucosa associated lymphoid tissue lymphoma) and gastric adenocarcinoma. It is also associated with certain extra-gastric disorders like immune thrombocytopenia and iron deficiency anaemia[3,4]. Although the role of these in causation of gastric injury has emerged in recent times, the role of *H. pylori* and its virulence factors in causation of atherosclerosis and coronary artery disease is not entirely clear as yet. The present review will focus on the relationship between this bacterium and the coronary artery disease

THE BACTERIUM

H. pylori have an inherent ability to survive in the gastric epithelium where they reside in the mucous layer and remain protected from the gastric acid. Urease, an enzyme abundantly present in this flagellate organism, helps create an alkaline environment to help in survival in the otherwise acidic environment. While most infected individuals remain unaffected, others develop a myriad of clinical manifestations ranging from gastritis to gastric cancer. What fuels and drives the pathogenesis of these varied clinical spectrums is not completely understood. While it is estimated that around half the world's population harbours infection with *H. pylori*, only a fraction of the infected manifest with the implicated diseases. The various factors implicated in disease causation following infection by *H. pylori* include both the bacterial virulence factors and the host response to the infection. The bacterial virulence factors include BabA (bacterial binding and inflammation), lipopolysaccharide (interaction with toll-like receptors and mediation of inflammation), Cag pathogenicity island (heightened inflammatory response to infection) and vacA toxin (impaired host responses). The host responses which affect the outcome of infection include interleukin (IL)-1β (certain polymorphisms associated with carcinogenesis), activation of nuclear factor (NF)-κB, IL-8 levels, recruitment of neutrophils, macrophages and oxidative injury and TH1 cell response may all mediate tissue injury and reaction to *H. pylori* infection.

CORONARY ARTERY DISEASE: A MULTIFACTORIAL DISEASE

Coronary artery disease (CAD) is a multifactorial disease manifesting in a number of clinical presentations including angina, myocardial infarction and heart failure. The CAD is primarily a result of coronary atherosclerosis for which a multitude of risk factors are implicated including hyperlipidemia, smoking, diabetes mellitus, lack of physical activity, male gender, increasing age, obesity amongst others[5]. There is a growing acknowledgement of inflammatory factors including C-reactive protein in prediction of increased risk of CAD[6]. *H. pylori* has also been implicated by some to have a role in predisposition to cardiac risk and causation of CAD. Indeed, in a polymerase chain reaction (PCR) based study for detection of *H. pylori* in the coronary plaques of patients who underwent coronary artery bypass grafting (CABG), 29.5% patients had a detectable *H. pylori* on PCR. Also there was serological evidence of infection in 53.3% of these 105 patients[7]. Therefore the infection by *H. pylori* may play a role in plaque rupture and causation of ischemic heart disease. Interestingly, cytotoxin asso-ciated gene A (Cag-A) may also play a role in the path-ogenesis of CAD as results of one study suggest that anti-Cag-A antibody titres were higher in patients with CAD vis-à-vis normal subjects. Also patients with anti-Cag-A positivity had more severe lesions of CAD[8]. It is believed that the chronic inflammation associated with chronic infections may result in progressive atherosclerotic disease eventually manifesting as CAD[9].

CAD AND *H. PYLORI*

Epidemiological evidence

A number of reports have evaluated the role of *H. pylori* in causation of CAD. In a report on 120 patients who underwent coronary angiography, the prevalence of serologically detectable evidence of *H. pylori* infection was more in patients with angiographically documented CAD (> 50% stenosis in at least one coronary artery). The evidence of infection was found in 70% patients with single vessel disease, 76.3% patients with double vessel disease but only in 50% individuals with no CAD[10]. Coronary artery calcium is believed to be a marker of atherosclerosis and its progression a predictor of CAD events. The correlation of coronary artery calcium (CAC) with various pathogens is conflicting. In a report on 201 asymptomatic subjects, the antibodies to heat shock protein 65 correlated with CAC score as also with evidence of *H. pylori* infection[11]. Another large study from South Korea which evaluated 2029 individuals for *H. pylori* antibody and coronary artery calcification score found that *H. pylori* seropositivity was different amongst those with and those without CAC[12]. This association was more evident in patients with early coronary atherosclerosis[12]. However another report about presence of *H. pylori* infection in a large cohort of individuals who underwent repeat CAC assessment, the presence of *H. pylori* infection (IgG to *H. pylori*) did not correlate with development or progression of CAC[13]. In a report comparing patients with CAD and healthy controls, sero-positivity for *H. pylori* infection was significantly higher

Table 1 Recent reports on association of *Helicobacter pylori* infection with coronary artery disease

Ref.	Population (number of subjects)	Diagnosis of CAD	Association between *H. pylori* infection and CAD
Shmuely *et al*[23]	CAD (173) *vs* Controls (123)	Myocardial Perfusion imaging	Yes No association with Cag-A
Vafaeimanesh *et al*[10]	CAD (62) *vs* Controls (58)	Angiographic	Yes
Laek *et al*[13]	5744 individuals, Age 45-84 yr, average follow-up of 2.4 yr	Newly detectable coronary artery calcium (CAC)	No correlation with CAC development
Mundkur *et al*[18]	CAD and controls (433 each) from South Asians	Angiography	None
Padmavati *et al*[24]	Acute myocardial infarction *vs* Controls	ECG, enzymes	None
Tewari *et al*[15]	200 CAD cases and controls	ECG, treatment records	Yes
Grdanoska *et al*[25]	Acute coronary syndrome (64), CAD (53), controls (35)	ECG, enzymes	Yes
Grub *et al*[26]	Controls (30), CAD (52) and CAD with rheumatic diseases (67)	Patients referred for CABG	None
Park *et al*[12]	2029 subjects	CAC	Yes
Al-Ghamdi *et al*[27]	CAD (50) and controls (15)	ECG, angiography	Yes
Azarkar *et al*[28]	Controls (78) and myocardial infarction (73)	ECG, enzymes	Yes
Khodaii *et al*[29]	Myocardial infarction (500) and controls (500)	ECG, enzymes	Yes Cag-A positivity also correlates with CAD

CAD: Coronary artery disease; Cag-A: Cytotoxin associated gene A; ECG: Electrocardiography; CAC: Coronary artery calcium; CABG: Coronary artery by-pass grafting; *H. pylori*: *Helicobacter pylori*.

in patients of CAD (59%) vis-à-vis the healthy controls (39%)[14]. Similar reports from India also corroborate that *H. pylori* sero-positivity was much higher in patients with CAD when compared with asymptomatic controls[15-17]. Few reports have indicated, to the contrary, that there is no significant association between *H. pylori* infection and CAD. In a report from Asian Indian families which evaluated role of multiple pathogens in causation of CAD, while CMV infection appeared to elevate the risk of CAD infection with *H. pylori* did not increase the risk[18]. In a large Japanese study to assess seroprevalence of *H. pylori* in CAD and asymptomatic controls no significant differences were detected between the two groups[19]. However when a subgroup of patients younger than 55 years was analysed the seroprevalence of *H. pylori* antibody was higher in cases than controls (58.7% and 43.3%, respectively)[19]. Another report about incidence of CAD in elderly individuals who were assessed for *H. pylori* infection at baseline and followed up for 10 years indicated that *H. pylori* positivity was not associated with increased incidence of CAD[20]. As described previously, PCR based studies of the coronary plaque have been done and have detected *H. pylori* DNA in them. In a controlled study of atheromatous plaques of 46 patients who underwent CABG, 22 (47.8%) showed *H. pylori* DNA while none of the controls who underwent coronary artery biopsy had PCR detectable *H. pylori*[21]. Aortic biopsies from areas free of atheromatous plaque have also been reported to be positive in a significant number of patients with CAD but none of the controls[22]. Table 1 summarises the recent studies reporting about association of *H. pylori* with CAD.

CAG-A AND CAD

As previously mentioned, role of Cag-A has also been evaluated as a predisposing factor for occurrence of coronary artery disease[8]. In a study of cardiac peptides including Brain Natriuretic Peptide in 103 patients with non-ST elevation myocardial infarction and their relation with *H. pylori* infection, it was found that individuals infected with Cag-A positive strains of *H. pylori* had higher levels of BNP in the serum[30]. BNP is a marker of heart failure and may predict a more serious course of the disease thereby suggesting that *H. pylori* infection with Cag-A positive strains may lead to an adverse outcome. Interestingly, IL-6 levels were also found to correlate with the Cag-A status. This suggests that the inflammatory response to Cag-A positive *H. pylori* may mediate atherogeneis in a subgroup of patients with CAD[30]. However other reports indicate that Cag-A positivity does not vary significantly between angiographically positive and negative group of individuals. In a report of 112 consecutive individuals who underwent coronary angiography, the Cag-A positivity did not affect the severity of CAD[31]. In a large study including 505 patients with CAD and 1025 matched controls, neither the prevalence of *H. pylori* infection was increased in the diseased subjects nor did the presence of Cag-A positive strains predict higher likelihood of CAD[32]. In a large population based report on 685 individuals, merely the presence of infection by *H. pylori* did not correlate with serum markers of inflammation. However those seropositive for Cag-A positive strains had increased values of common carotid artery intima-media thickness and the risk of atherosclerosis was enhanced by CRP positivity[33]. Another report also indicated that Cag-A positive strains appeared to raise the risk of CAD while merely the presence of *H. pylori* infection was not significantly different between cases and controls[34]. An

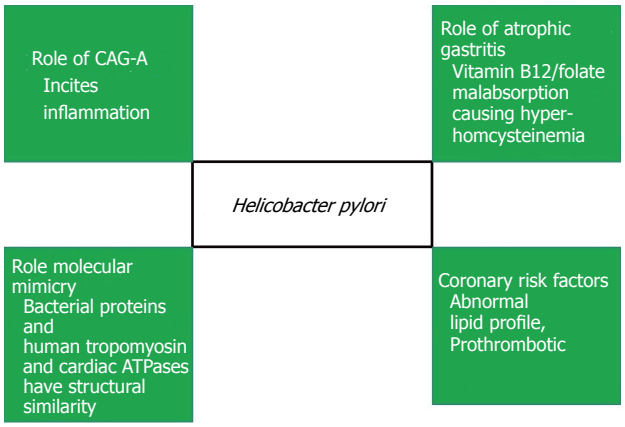

Figure 1 Postulated mechanisms of Atherogenesis in *Helicobacter pylori* infection.

interesting study reported about sero-prevalence of anti-Cag-A antibodies across a spectrum of presentations which included controls, stable and unstable angina and found that anti-Cag A titres were significantly higher in patients with unstable angina[35].

MECHANISMS BEHIND ATHEROGENESIS

One report has studied the association of atrophic gastritis with CAD. Atrophic gastritis is believed to be the end result of chronic gastric inflammation including that related to *H. pylori* infection. Decrease in serum pepsinogen I and a low Pepsinogen I / Ⅱ ratio points to the diagnosis of atrophic gastritis. In this intriguing report based on a population based study, Senmaru *et al*[36] reported that prevalence of CAD was higher in the patients having atrophic gastritis (5.8%) when compared with individuals not having atrophic gastritis (2.8%). Atrophic gastritis may result in malabsorption of Vitamin B12 and Folate and result in increased homocysteine levels. Hyper-homocysteinemia is a recognised risk factor for CAD[37]. One report has also suggested structural homology between bacterial proteins and human tropomyosin and cardiac ATPases thereby providing insight into molecular mechanism involved in the cardiac injury due to anti-*H. pylori* inflammatory response[30]. *H. pylori* has also been associated with dyslipidemia. In a Japanese study on 6289 subjects, infection with *H. pylori* was associated with low HDL and elevated LDL levels[38]. Other reports have also provided similar evidence[39]. Cag-A positive strains also exhibit elevated levels of highly sensitive CRP, oxidized LDL and apolipoprotein B all of which may participate in the pathogenesis of atherosclerosis[40]. There is also a suggestion that *H. pylori* may have a prothrombotic role which may also increase the associated risk of atherosclerotic diseases. The bacterium may promote aggregation of platelets by binding to the von-Willibrand factor[41]. Infection with *H. pylori* may stimulate an inflammatory response against heat shock protein (hsp60) which may drive a helper T cell (TH1) response and increase the risk of atherosclerosis[42]. The high degree of homology between bacterial and eukaryotic HSP may result in molecular mimicry and collateral immune damage from immune response primarily directed against infectious agents[43]. The host reaction to the *H. pylori* lipopolysaccharide (LPS) may also be a risk factor for atherosclerosis[44]. Figure 1 depicts the predominant mechanisms purported to play a role in genesis of *H. pylori*-related CAD.

EFFECT OF ERADICATION

The prognostic role of *H. pylori* infection has also been assessed in acute CAD. In 433 patients of acute coronary syndrome (ACS) the seroprevalence of *H. pylori* infection was determined using IgG and IgA serology. Those infected with *H. pylori* had an increased risk of short term adverse outcomes during the first month of follow-up[45]. Another report which evaluated role of eight pathogens on occurrence future events in patients diagnosed to have angiographic evidence of CAD. Serological evidence of *H. pylori* infection predicted an increased risk of future events and mortality in these 1018 patients and increase in pathogen burden also affected long term outcome[46]. An interesting study evaluated the role of *H. pylori* eradication on coronary artery lumen reduction in patients who underwent percutaneous intervention for CAD. A higher loss of coronary lumen was noted in those patients who had serological evidence of *H. pylori* infection. Also, eradication of *H. pylori* attenuated this reduction in lumen of the coronary artery vis-à-vis the placebo group[47]. Another report by the same group provides similar findings but it is not clear if the report was based on different patients[48]. This small but elegant study opens debate about possible benefit of *H. pylori* eradication in attenuating further atherosclerotic process which is driven primarily by inflammatory mediators. In a study assessing the effect of *H. pylori* eradication on coronary risk factors in 48 patients, no differences were observed in pre and post-treatment fasting sugars, lipid profile and levels of tissue-plasminogen activator, fibrinogen, plasminogen activator inhibitor-1 and D-dimer levels[49]. However a larger study of 496 patients and reporting about pre and post- *H. pylori* eradication profile, the eradication of *H. pylori* seemed to increase HDL levels and reduce the levels of C reactive protein and those of fibrinogen. This suggests that attenuation of inflammatory response is likely to occur after *H. pylori* eradication[50]. In a report documenting the effects of *H. pylori* eradication on insulin resistance in 159 patients using homeostasis model assessment of insulin resistance, the insulin resistance measured six weeks post-eradication was lower than the baseline. The study also reported changes in lipid profile including an increase in HDL levels and a fall in LDL levels with *H. pylori* eradication[51]. Another report also indicates that the *H. pylori* eradication may increase HDL levels and lead to reduction of CRP levels[52]. Table 2 depicts various studies reporting about the effects of *H. pylori* eradication on CAD and its risk

Table 2 Effect of *Helicobacter pylori* eradication on coronary artery disease

Ref.	Population	Intervention	Results
Kowalski *et al*[47,48]	40 patient with single vessel CAD and *H. pylori* infection	All underwent PTCA and 20 each received eradication or placebo	Attenuated reduction mean coronary artery lumen at 6 mo in those undergoing eradication
Lu *et al*[49]	*H. pylori* positive individuals	Testing of coronary risk factors before and after *H. pylori* eradication	No change in sugar, lipid and fibrinolytic parameters with eradication
Pellicano *et al*[50]	*H. pylori* positive individuals	Testing of coronary risk factors before and after *H. pylori* eradication	Improvement in HDL-C, reduction in CRP and fibrinogen levels. Elevation in BMI and diastolic blood pressure
Gen *et al*[51]	*H. pylori* positive individuals	Testing for insulin resistance, lipid profile and CRP before and after eradication	Improvement in insulin resistance, lipid abnormalities and CRP levels
Kanbay *et al*[52]	*H. pylori* positive individuals	Testing for lipid profile and CRP before and after eradication	Increase in HDL and reduction in CRP with successful eradication

CAD: Coronary artery disease; CRP: C-reactive protein; HDL: High density lipoprotein; PTCA: Percutaneous transluminal coronary angioplasty; *H. pylori*: *Helicobacter pylori*.

factors.

ATHEROGENESIS BEYOND CORONARY ARTERIES

In contrast to CAD, data is scarce on the relation between *H. pylori* infection and stroke. A meta-analysis found that Cag-A-positive *H. pylori* increases the risk of both ischemic stroke and coronary heart disease[53].

A case-control study of 150 patients by Yang *et al*[54] in 2011 does not reveal any strong association between chronic *H. pylori* infection and ischemic stroke. However, another study by Pan[55] suggested lowering of inflammatory markers and decrease in cerebral infarction readmission rates in patients of stroke with positive urease test treated with (conventional therapy + anti- *H. pylori* therapy. Wu *et al*[56] suggested role of increased expression of CD62p on platelets and increase in clotting indexes in pathogenesis of stroke in *H. pylori* positive patients.

A meta-analysis of 13 studies including 4041 participants indicated that positive anti-*H. pylori* IgG, anti-Cag-A IgG and (13)C-urea breath test were significantly associated with increased risk of IS, respectively, and positive anti-Cag-A IgG was more effective for predication of IS risk[57].

But a formal meta-analysis of ten prospective observational studies indicated no strong association between *H. pylori* infection and stroke, neither in those with cytotoxin-associated gene-A-positive infection[58].

All in all, the evidence supporting the role of *H. pylori* in causation of CAD is equivocal and interventions aimed at *H. pylori* eradication have not shown conclusive evidence of benefit in eradicating the organism vis-à-vis cardiovascular outcomes. Perhaps multicentre randomised trials comparing eradication of *H. pylori* in large populations at risk of CAD and then follow-up to deterimine risk of CAD may answer this question.

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P- Reviewer: Peteiro J, Schoenhagen P **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Cardiology

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DOI: 10.4330/wjc.v7.i1.26

World J Cardiol 2015 January 26; 7(1): 26-30
ISSN 1949-8462 (online)
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MINIREVIEWS

Relationship between vascular endothelium and periodontal disease in atherosclerotic lesions: Review article

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Supported by The Fundo de Incentivo à Pesquisa e Eventos (FIPE) at Hospital de Clínicas de Porto Alegre, No. HCPA-120265.
Conflict-of-interest: The authors declare they do not have any competing interest related to this study.
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Received: September 25, 2014
Peer-review started: September 25, 2014
First decision: October 21, 2014
Revised: November 26, 2014
Accepted: December 18, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

Inflammation and endothelial dysfunction are linked to the pathogenesis of atherosclerotic disease. Recent studies suggest that periodontal infection and the ensuing increase in the levels of inflammatory markers may be associated with myocardial infarction, peripheral vascular disease and cerebrovascular disease. The present article aimed at reviewing contemporary data on the pathophysiology of vascular endothelium and its association with periodontitis in the scenario of cardiovascular disease.

Key words: Endothelium; Vascular; Atherosclerosis; Periodontal diseases; Nitric oxide; Cardiovascular diseases

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Core tip: Recent studies underscore the importance of endothelial dysfunction and inflammatory markers for the development of atherosclerotic disease. In addition, the literature suggests a direct association between periodontal and cardiovascular diseases. Nevertheless, more robust intervention studies are required to clarify specific gaps, especially in relation to the biological and clinical effects of periodontal disease on the genesis and progression of atherosclerotic disease.

Saffi MAL, Furtado MV, Polanczyk CA, Montenegro MM, Ribeiro IWJ, Kampits C, Haas AN, Rösing CK, Rabelo-Silva ER. Relationship between vascular endothelium and periodontal disease in atherosclerotic lesions: Review article. *World J Cardiol* 2015; 7(1): 26-30 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/26.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.26

INTRODUCTION

Cardiovascular disease is still the leading cause of morbidity and mortality worldwide. Nevertheless, as a

result of new and effective strategies to prevent and treat atherosclerosis, the number of deaths associated with cardiovascular events has not increased, and seems to have stabilized in some countries[1].

Because it has regulatory, secretory, metabolic, immunological, and synthesizing properties, the vascular endothelium may be regarded as a heterogeneous and dynamic organ. An imbalance of these properties is linked to the onset of endothelial dysfunction and atherogenesis, and to increased risk of cardiovascular events[2]. Added to that, in the past years, the role of inflammation in the development of atherosclerosis has also been explored. Data from epidemiologic studies confirm the association between high levels of inflammatory markers and the progression of cardiovascular disease[3,4].

Emerging evidence suggests that periodontal infection may be an independent risk factor for myocardial infarction, peripheral vascular disease, and cerebrovascular disease[5,6]. A metanalysis has shown increased incidence of coronary heart disease [relative risk (RR) = 1.14; 95%CI: 1.07-1.21; $P < 0.001$] in patients with periodontal disease even after adjustment for confounding factors such as smoking, diabetes, alcohol intake, obesity, and arterial hypertension, also suggesting a positive correlation between dental loss and coronary artery disease[6]. It should be noted that much of this evidence was generated by observational studies. In this sense, additional studies with more robust designs should be carried out to provide answers regarding the association between periodontal and cardiovascular diseases.

With the aim of furthering the understanding of the relationship between vascular endothelium, periodontal disease, and the process of atherosclerosis, this article will review contemporary data about endothelial pathophysiology and its association with periodontitis in cardiovascular disease. For that, the MEDLINE-PubMed database was searched to retrieve articles published between 1980 and 2014, using the following DeCS terms: "endothelium, vascular"; "atherosclerosis"; "periodontal diseases"; "nitric oxide"; "cardiovascular diseases".

VASCULAR ENDOTHELIUM AND ATHEROSCLEROSIS

Endothelial cells (ECs) form an organ weighing approximately 1 kg; they are distributed along the body (total estimated area: 7000 m^2), and are characterized by heterogeneous structure and function, with phenotypic variation according to their location in different organs, tissues, or blood vessel type[7]. Located at the interface between blood and tissues, the vascular endothelium plays an important role in the cardiovascular system, including regulation of vascular tone (smooth muscle), synthesis and secretion of molecules, and control of homeostasis, coagulation, and inflammatory and atherogenic responses[8].

Atherosclerosis is a progressive disease, characterized by accumulation of lipid particles and fibrous elements on the arterial wall. A more recent concept has introduced the notion that, in addition to the thrombotic process, inflammation and endothelial dysfunction are also directly related to all stages of atherosclerosis. In the undamaged endothelium, ECs resist leukocyte adhesion and aggregation, in addition to promoting fibrinolysis. However, when associated with inflammatory factors, such as periodontal disease, cardiovascular risk factors (smoking, obesity, sedentary lifestyle, dyslipidemia, diabetes) promote changes in endothelial permeability and hence endothelial function[9]. At this initial stage, ECs express adhesion molecules that selectively recruit various leukocyte classes into the tunica intima[10]. Monocytes mature into macrophages, forming foam cells that release cytokines and factors that affect ECs. This process induces migration of smooth muscle cells from the media to the intima and affects metabolism of the arterial extracellular matrix (metalloproteinase), synthesis and release of procoagulant factors, and the bioavailability of nitric oxide (NO)[9]. NO, initially defined by Furchgott *et al*[11] as an "endothelium-derived relaxing factor", is synthesized by the action of an enzyme, endothelial nitric oxide synthase (eNOS), from the amino acid L-arginine. NO plays a fundamental part in endothelial function, promoting smooth muscle relaxation and consequently vasodilatation. In addition, NO supports inhibition of platelet aggregation, smooth muscle cell proliferation, and maintenance of anti-sclerotic effect[12].

The inflammatory process may also contribute to atherosclerotic plaque rupture and thrombosis. Inflammation regulates the fragility of the fibrous cap and the thrombogenicity of the atherosclerotic plaque, influencing collagen metabolism, which provides strength and stability to the cap[13]. Pro-inflammatory cytokines such as C-reactive protein (CRP), fibrinogen, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 reduce the endothelial expression of NOS[14], increasing endothelial synthesis of NADPH oxidases and promoting endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and P-selectin[14,15]. As a result, the absence of anti-atherogenic properties in the endothelium increases leukocyte migration and platelet activation to form the atherosclerotic plaque[4].

In this sense, endothelial function and inflammatory markers are important predictors of future cardiovascular events in individuals at risk for atherosclerotic disease.

CELL ADHESION MOLECULES

Cell adhesion molecules (CAMs) are glycoproteins expressed on the cellular surface. CAMs are involved in cell-cell and cell-extracellular matrix binding and encompass immunoglobulins such as ICAM-1 and VCAM-1, as well as the selectin family, including leukocyte-endothelial adhesion molecules (E-selectin), P-selectin and leukocyte-lymphocyte adhesion molecules (L-selectin), integrins, and cadherins[16].

Selectins are expressed on the surface of endothelial

Table 1 Summary of the involvement of pro-inflammatory cytokines and adhesion molecules in atherosclerosis

Pro-inflammatory cytokines and adhesion molecules	Cells involved	Atherogenic effect
C-reactive protein	Adhesion molecules and endothelial cells	Stimulates production of adhesion molecules and chemokines by endothelial cells[14]
Fibrinogen	Platelet, adhesion molecules and smooth muscle	Activates platelet aggregation and promotes the migration and proliferation of smooth muscle[14]
Tumor necrosis factor-alpha	Monocytes, neutrophils and endothelial cells	Activates monocytes, neutrophils and endothelial cells to express adhesion molecules[14]
Interleukin-6	Epithelial cells, fibroblasts and macrophages/monocytes	Is involved in promoting coagulation, which result in the development of atherosclerosis[14]
Interleukin-1β	Macrophages/monocytes	Impedes fibrinolysis, facilitates coagulation and thrombosis[14]
Vascular cell adhesion molecule-1	Endothelial cells	Suggested as potential candidate markers of endothelial dysfunction[19]
Intercellular adhesion molecule-1	Endothelial cells	Implicated in leukocyte recruitment and migration into the vessel wall[19]
Leukocyte-endothelial adhesion molecules	Endothelial cells	Migration of monocytes down into the subendothelial space[16]

cells, leukocytes, and platelets, and their expression in the endothelium is induced by various inflammatory cytokines. In the first phase of leukocyte migration, selectins mediate the capture and transport of circulating leukocytes into the vascular endothelium. In the second phase, leukocytes adhere to the endothelium through the action of ICAM-1 and VCAM-1, migrating into the interstitial tissue space[17].

Soluble forms of CAMs are found in plasma and correlate to endothelial dysfunction[18]. Thus, these markers are associated with biological mechanisms that promote thrombus formation, plaque rupture, and subsequently acute coronary events[19]. The summary of the involvement of pro-inflammatory cytokines and adhesion molecules in atherosclerosis is described in Table 1.

SHEAR STRESS

Even if the multifactorial pathophysiologic nature of atherosclerosis is recognized, special attention should be paid to a specific component in this scenario-shear stress. Shear stress is a biomechanical force determined by blood flow, vessel geometry, and fluid viscosity, aspects modulating the structure and function of the vascular endothelium. The presence of "disturbed" flow-that is, nonlaminar flow-favors atherosclerotic plaque formation. Atherosclerotic plaque development is favored by a combination of cardiovascular risk factors and altered arterial hemodynamics around curvatures, arterial branch ostia and bifurcations[20].

Studies have shown that different types of shear stress correlate with "resistant" or "susceptible" regions in the endothelium during atherogenesis[21]. Pulsatile blood flow triggers many types of hemodynamic, hydrostatic, and cyclic forces that have the ability to influence vascular endothelial physiology[22]. The most susceptible atherosclerotic lesions are associated with certain sites in the proximal branches, bifurcations, and in areas of greater curvature. However, regions with uniform laminar flow are typically more resistant to atherogenic plaque formation[23].

PERIODONTAL DISEASE, INFLAMMATORY MARKERS, AND ENDOTHELIAL DYSFUNCTION

Periodontal disease encompasses two large groups of gum diseases. Gingivitis, which is characterized by inflammation of the gingival margin, is easily reversed with adequate oral hygiene. Periodontitis entails a chronic infectious/inflammatory process involving the supporting tissues of the tooth, including periodontal ligament and alveolar bone. The main consequence of periodontitis is the loss of tooth support structures and tooth loss[24]. Data from different countries show a prevalence of periodontitis reaching up to 50%[25-27]; however, progression is usually slow[28].

Epidemiologic studies provide evidence of an association between periodontitis and cardiovascular disease[6,29]. The biological plausibility for this association is based mainly on the fact that patients with periodontitis present increased levels of CRP, TNF-α, interleukins, and other inflammatory markers, which are associated with endothelial dysfunction and cardiovascular events[30,31]. Most studies employ different inflammatory and endothelial biomarkers, with secondary outcomes, whereas primary outcomes such as death or brain stroke have not yet been evaluated[32-34].

A recent systematic review and metanalysis analyzed the effect of periodontal treatment on cardiovascular risk profile in patients with established periodontitis. The main findings show a significant reduction in CRP (-0.50 mg/dL), IL-6 (-0.48 ng/L), TNF-α (-0.75 pg/mL), fibrinogen (-0.47 g/L) and total cholesterol (-0.11 mmol/L) in the intervention group. In addition, there was improvement of endothelial function and an additional benefit regarding inflammatory markers in patients with traditional cardiovascular risk factors[24]. Investigating the same outcome in a different scenario, another study compared patients with coronary heart disease with or without periodontitis. The results indicate that treatment of periodontal disease promoted a reduction in serum concentrations of CRP, from 2.7 ± 1.9 mg/L to 1.8 ± 0.9 mg/L ($P < 0.05$), and of IL-6, from 2.6 ± 3.4 mg/L to 1.6

Table 2 Summary of the effects of periodontal disease on pro-inflammatory cytokines and adhesion molecules

Pro-inflammatory cytokines and adhesion molecules	Effect of periodontal disease
C-reactive protein	Increased[24]
Fibrinogen	Increased[24]
Tumor necrosis factor-alpha	Increased[24]
Interleukin-6	Increased[24]
Interleukin-1β	Increased[24]
Vascular cell adhesion molecule-1	Increased[30]
Intercellular adhesion molecule-1	Increased[30]
Leukocyte-endothelial adhesion molecules	Increased[30]

± 2.6 mg/L ($P < 0.05$) in patients with periodontitis[32].

In addition to inflammatory markers and adhesion molecules, the measurement of brachial artery flow-mediated dilation (FMD), a technique developed initially in 1992, is also useful to assess the endothelium[35]. This non-invasive technique evaluates the diameter of the brachial artery before and after induced forearm ischemia. A blood pressure cuff is inflated at the distal or proximal section of the arm, and FMD is expressed as the percent change in brachial artery diameter at the end of ischemia. This dilatation is mediated by endothelial release of NO in response to shear stress at the arterial wall[36].

FMD is decreased in individuals with cardiovascular risk factors (diabetes, hypertension, obesity, and smoking, among others) and established atherosclerosis[37]. A study published in 2005 evaluated endothelial function in patients with a diagnosis of severe periodontitis. The main findings following periodontal treatment show significant improvement in FMD, of 9.8% ± 5.7% ($P = 0.003$) as compared to baselines measures, accompanied by a reduction in the levels of CRP from 1.1 ± 0.9 to 0.8 ± 0.8 ($P = 0.026$)[34]. In this sense, evaluation of FMD and cardiovascular disease biomarkers have recently been studied and associated with endothelial dysfunction and occurrence of cardiovascular events[38,39]. The summary of the effects of periodontal disease on pro-inflammatory cytokines and adhesion molecules is depicted in Table 2.

CONCLUSION

The present literature review suggests that periodontal treatment reduces the risk of cardiovascular disease by improving plasma levels of inflammatory markers (CRP, TNF-α, IL), thrombotic markers (fibrinogen) and adhesion molecules (VCAM-1, ICAM-1, P-selectin), in addition to improving endothelial function as assessed by FMD. Future intervention studies are required to further elucidate the association between periodontal and cardiovascular disease, especially in terms of the biological effects of periodontal disease on the atherogenic cascade affecting the vascular endothelium.

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P- Reviewer: Barzilay JI, Guzman-Gutierrez E **S- Editor**: Ji FF
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World Journal of Cardiology

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DOI: 10.4330/wjc.v7.i1.31

World J Cardiol 2015 January 26; 7(1): 31-42
ISSN 1949-8462 (online)
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ORIGINAL ARTICLE

Case Control Study

End-organ protection in hypertension by the novel and selective Rho-kinase inhibitor, SAR407899

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Author contributions: Löhn M performed the majority of experiments, designed the study and wrote the manuscript; Plettenburg O, Hofmeister A and Kadereit D designed and synthetized SAR407899; Kannt A performed an initial compound screening; Kohlmann M performed the pharmacokinetics of SAR407899; Monecke P and Schiffer A were involved in structural biology and modeling required for the compound optimization; Schulte A performed the histology; Ruetten H and Ivashchenko Y were also involved in writing and editing the manuscript.

Ethics approval: All animal experiments were performed in accordance with the German law for the protection of animals and current Aventis Laboratory Animal Science and Welfare (LASW) guidelines.

Informed consent: Not applicable.

Conflict-of-interest: There is no conflict-of-interest to disclose. All authors are employees of Sanofi-Aventis Deutschland GmbH.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at Matthias.loehn@sanofi.com. Participants gave informed consent for data sharing. No additional data are available.

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Received: July 14, 2014
Peer-review started: July 15, 2014
First decision: November 3, 2014
Revised: December 12, 2014
Accepted: December 29, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

AIM: To compare the therapeutic efficacy of SAR407899 with the current standard treatment for hypertension [an angiotensin converting enzyme (ACE)-inhibitor and a calcium channel blocker] and compare the frequency and severity of the hypertension-related end-organ damage.

METHODS: Long-term pharmacological characterization of SAR407899 has been performed in two animal models of hypertension, of which one is sensitive to ACE-inhibition and the other is insensitive [deoxycorticosterone acetate (DOCA)]. SAR407899 efficiently lowered high blood pressure and significantly reduced late-stage end organ damage as indicated by improved heart, kidney and endothelial function and reduced heart and kidney fibrosis in both models of chronic hypertension.

RESULTS: Long term treatment with SAR407899 has been well tolerated and dose-dependently reduced elevated blood pressure in both models with no signs of tachyphylaxia. Blood pressure lowering effects and protective effects on hypertension related end organ damage of SAR407899 were superior to ramipril and amlodipine in the DOCA rat. Typical end-organ damage was significantly reduced in the SAR407899-treated animals. Chronic administration of SAR407899 significantly reduced albuminuria in both models. The beneficial effect of SAR407899 was associated with a reduction in leukocyte/macrophage tissue infiltration. The overall protective effect of SAR407899 was superior or comparable to that of ACE-inhibition or calcium

channel blockade. Chronic application of SAR407899 protects against hypertension and hypertension-induced end organ damage, regardless of the pathophysiological mechanism of hypertension.

CONCLUSION: Rho-kinases-inhibition by the SAR407899 represents a new therapeutic option for the treatment of hypertension and its complications.

Key words: Hypertension; End organ damage; Rho-kinase; Angiotensin converting enzyme-inhibition

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Core tip: Rho-kinase (ROCK) is considered an important ta-rget in cardiovascular diseases, *e.g.*, hypertension and nephropathy. Currently available treatment only moderately alleviates the progression of chronic kidney diseases. We have identified a novel, potent and selective inhibitor of ROCK (SAR407899) and characterized its effects *in vivo*. The therapeutic efficacy of SAR407899 has been compared to the current standard treatment for hypertension in two animal models of hypertension, one of which is sensitive and the other insensitive (deoxycorticosterone acetate) to angiotensin converting enzyme-inhibition. ROCK-inhibition by SAR407899 may represent a new therapeutic option either as a monotherapy or in combination with existing modern therapeutics for the treatment of hypertension and its complications.

Löhn M, Plettenburg O, Kannt A, Kohlmann M, Hofmeister A, Kadereit D, Monecke P, Schiffer A, Schulte A, Ruetten H, Ivashchenko Y. End-organ protection in hypertension by the novel and selective Rho-kinase inhibitor, SAR407899. *World J Cardiol* 2015; 7(1): 31-42 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/31.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.31

INTRODUCTION

Hypertension increases the risk of target organ damage, including heart hypertrophy, heart ischemia, kidney dysfunction or failure, cerebrovascular events and malfunction of the endothelial tissue[1-5]. The contractile response of smooth muscle tissue is controlled at different levels by a tight balance of pro-contractile and relaxing mechanisms. In particular, it has been persuasively shown that Rho-kinases (ROCK1 and ROCK2) are intimately involved in the transmission of contractile signaling within smooth muscle tissue[6-13]. Upon activation of the small GTPase RhoA by ligand-bound specific GPCRs, ROCKs, the downstream effectors of RhoA, phosphorylate the myosin light chain phosphatase and the myosin regulatory light-chain itself, resulting in a net increase in activated myosin. This promotes smooth muscle contraction and actin cytoskeleton re-organization. Inhibition of ROCKs leads to relaxation of vascular smooth muscle cells and, consequently, to a decrease in blood pressure[7,9,14-20]. Several inhibitors of ROCK (in particular, fasudil and Y27632) have been extensively used to evaluate the role of ROCK in cardiovascular physiology and pathology. In addition, fasudil is used in Japan to treat cerebral vasospasm after focal cerebral ischemia or aneurysmal subarachnoid hemorrhage. However, both inhibitors have a moderate specificity, moderate potency and short duration of action *in vivo* that limit their clinical use. Therefore, the development of a more potent and specific inhibitor with a better pharmacokinetic profile is needed to explore the potential of ROCK inhibition in the therapy of hypertension and its complications. We have identified a novel ROCK-inhibitor, SAR407899, and previously characterized its acute effects *in vitro* and *in vivo*[21]. Here, we describe the long-term effects of SAR407899 treatment in two animal models of hypertension, one being sensitive (Nω-Nitro-L-arginine methyl ester hydrochloride, LNAME) and the other being insensitive [deoxycorticosterone acetate (DOCA)] to angiotensin converting enzyme (ACE)-inhibition. The DOCA-induced hypertension model is characterized by a hypervolemic and low plasma renin status, which promotes resistance to ACE-inhibition, whereas the LNAME model is normovolemic and displays a high renin activity in plasma[22-24]. The results of large clinical trials (IDNT, RENAAL and IRMA-2) revealed that the current standard treatment only modestly (approximately 20%) reduces the progression of chronic kidney diseases. From these data it can be concluded that a simple decrease of blood pressure is not sufficient for kidney protection. Our results indicate that chronic inhibition of the ROCK kinases efficiently controls blood pressure and significantly reduces the frequency and severity of the hypertension-related end organ damage.

MATERIALS AND METHODS

DOCA and LNAME-induced hypertension

Adult male Sprague Dawley rats (190 to 210 g, Harlan Winkelmann, Borchen, Germany), were treated with DOCA-salt or Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME) to induce hypertension. To compare the pharma-cological potency of ROCK-inhibition with the current anti-hypertension drugs, the individual blood pressure lowering effect of the respective compounds was measured in spontaneous hypertensive rats (SHR). Oral application of SAR407899 at 3 mg/kg lowered blood pressure in conscious telemetred SHR by 26 ± 4 mmHg (n = 10), which was comparable to the action of amlodipine at 3 mg/kg (blood pressure reduction by 33 ± 8 mmHg, n = 10) and ramipril at 1 mg/kg (blood pressure reduction by 21 ± 7 mmHg, n = 10). Therefore, the animals were divided into the following groups: (1) Control; (2) DOCA or LNAME; (3) DOCA or LNAME + SAR407899 at 3 mg/kg; (4) DOCA or LNAME + SAR407899 at 10 mg/kg;

(5) DOCA or LNAME + ramipril at 1 mg/kg; and (6) DOCA or LNAME + amlodipine at 3 mg/kg. All DOCA-salt treated animals underwent a unilateral nephrectomy, received a subcutaneous injection of DOCA (30 mg/kg; Sigma Chemical, St. Louis, MO, United States) dissolved in sesame oil once a week and 1% NaCl in the drinking water ad libitum. All LNAME groups received 40 mg/kg per day LNAME in the drinking water *ad libitum*. After a 4-wk treatment, the animals were placed into metabolic cages and 24 h-urine samples and blood samples were taken to analyze kidney function. Urinary and plasma creatinine levels were determined using standard kits (Roche diagnostics, Basel, Switzerland) on a Hitachi 912 E analyzer (Hitachi, Mountain View, Calif., United States). Urinary albumin was measured using a standard kit from Progen (Mikroflural, Progen, Heidelberg, Germany) and was normalized to urinary creatinine concentrations. After 5 wk of treatment, measurements of: (1) blood pressure (invasively, two hours after the last treatment); (2) organ weights; and (3) endothelial function were taken. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the United States National Institutes of Health (NIH publication no. 85-23, revised 1996).

Invasive blood pressure measurement

The animals were anaesthetized with an intraperitoneal injection of thiopental (0.1 g/mL per 100 g body weight). The common carotid artery was catheterized with a heparinized microcatheter (diameter 1.6 mm, Vycon, France). Blood pressure was measured with a Hugo Sachs hemodynamic system (March-Hugstetten, Germany) using the software Hemodyn.

In vitro vascular and heart function

Assessment of *in vitro* vascular function was performed as described earlier[21,25,26]. Heart function was determined using a Langendorff-setup in the working heart perfusion mode. This technique allows the heart to perform its physiological pumping action, *i.e.*, it performs pressure/volume work. The working heart technique therefore provides a complete analysis of heart function. Heart power is an integrative parameter and is calculated by formula (1):

$$HW\ (J) = 133.3\ [(N/m^2)/mmHg] \times (ALPmean\text{-}PLPmean)\ (mmHg) \times SV\ (m^3) + 0.5 \times 1.004\ (kg/m^3) \times SV\ (m^3) \times \{SV\ (m^3)/[\pi \times r^2\ (m^2) \times ET\ (s)]\}^2 \quad (1)$$

where HW-heart power, ALPmean-afterload pressure, PLPmean-preload pressure, SV-stroke volume, and ET-Ejection time. If not otherwise indicated, chemicals were obtained from Sigma (Deisenhofen, Germany).

RT PCR

Real-time quantitative PCR was performed using the QuantiTect Probe RT-PCR Kit (Qiagen, Hilden, Germany). Each sample was assayed in quadruplicate. For relative quantification of gene expression, the ΔCt method was used with GAPDH as a control. Amplification of the target and housekeeping genes was detected simultaneously using differently fluorescent-labeled Taq Man probes (Col1A1: Rn00801665_g1, CD3: Rn01417941_g1 and CD68: Rn01495634_g1), which were obtained from Applera/Applied Biosystems (Foster City, United States). Amplification linearity of the target and housekeeping genes within the multiplex RT-PCR was assessed by performing RT-PCR reactions with dilutions of the templates. RT-PCR reactions and data acquisition was performed using the iCycler-iQ-Thermocycler (Bio-Rad Laboratories GmbH, Munich, Germany). Relative gene expression was calculated as fold induction *vs* control samples.

Histology

Heart and kidneys underwent a standard fixation procedure and standard haematoxylin-eosin and sirius red staining. The hearts and kidneys were analyzed with regard to incidence and extent of fibrosis, inflammatory events, glomerulosclerosis and tubular atrophy. A semi-quantitative score was assigned to each specimen by an experienced pathologist ranging from 1 (minimal changes) to 4 (marked alterations) at a standard magnification of 4 to 20-fold. All histopathological analyses were performed in a blinded fashion. Anti-podocin staining was performed using anti-podocin antibodies (Sigma-Aldrich, United States).

Statistical analysis

All values are given as the mean and standard error of mean. Normality of the distribution and the homogeneity of variance were checked using the Levene test. For group comparisons, one-way analysis of variance (*ANOVA*) or two-way ANOVA was performed followed by Dunnett's post-hoc test using the SAS version 8.2 software. Differences between groups were considered significant if $P < 0.05$; n represents the number of specimens or animals tested.

The statistical methods of this study were reviewed by and complies to the standard of Sanofi-Aventis GmbH Deutschland.

RESULTS

Effect of SAR407899 on body weight, blood pressure and kidney function

The long-term effects of SAR407899 in DOCA- and LNAME-induced hypertension were compared to those of the current standard anti-hypertensive drugs, namely ramipril (ACE-inhibitor) and amlodipine (calcium channel blocker, CCB). Figure 1 depicts the effects of SAR407899 on body weight of the DOCA- and LNAME-hypertensive animals. Treatment with SAR407899 was well tolerated and showed a significant protective effect on body weight in both hypertensive animal models (Figure 1A and C). Factors involved in the continuous body weight loss are not known and most likely depend on hypertension related end-organ damage,

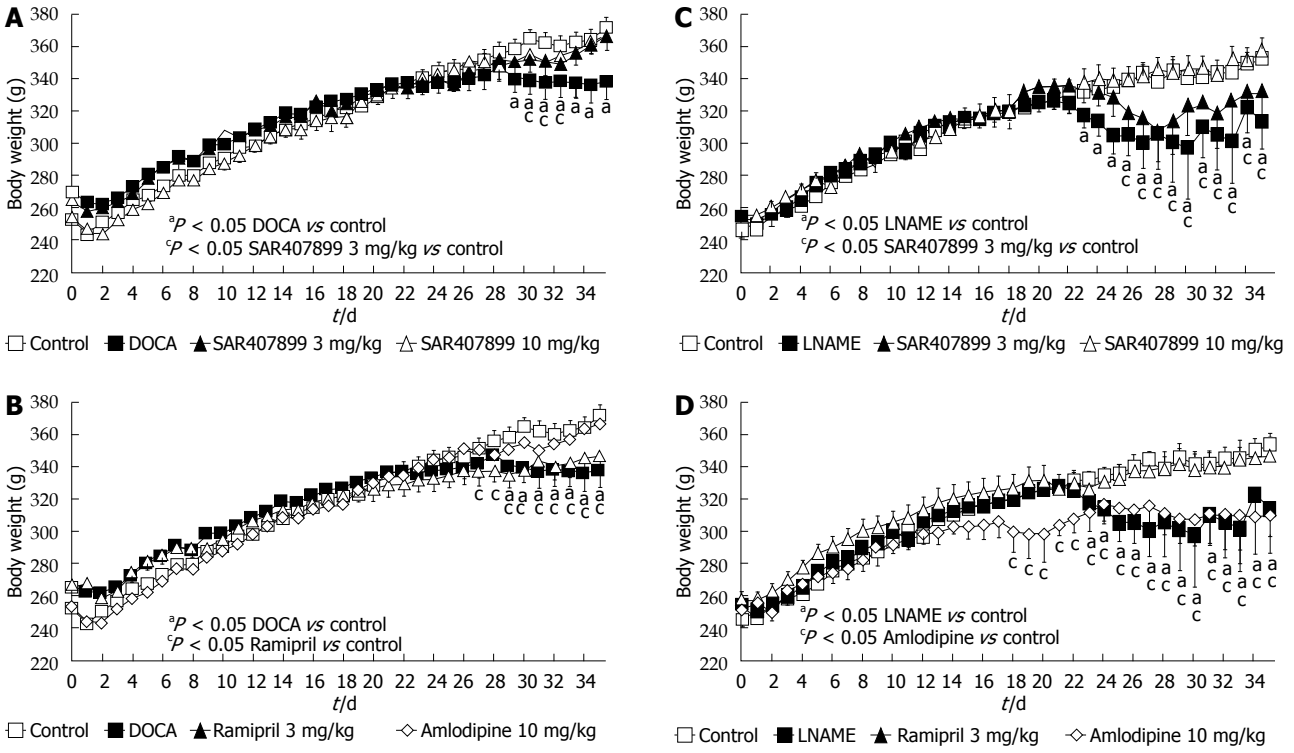

Figure 1 Effect of SAR407899 on body weight in deoxycorticosterone acetate and Nω-Nitro-L-arginine methyl ester hydrochloride hypertensive animals. A and B: Body weight of deoxycorticosterone acetate (DOCA) rats. A significant decrease in body weight was observed after 28 d; A: Effect of SAR407899 at 3 mg/kg and 10 mg/kg on body weight. Both doses protected DOCA rats against body weight loss; B: Effect of ramipril at 1 mg/kg and amlodipine at 3 mg/kg on body weight. Only amlodipine showed protective effects on body weight loss; C and D: Body weight of Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME) rats. A significant decrease in body weight was observed after 22 d. C: SAR407899 at 10 mg/kg significantly protected LNAME rats from body weight loss; D: Effect of ramipril at 1 mg/kg and amlodipine at 3 mg/kg on body weight. Only ramipril showed significant protective effects on body weight loss.

including proteinuria. Ramipril showed protective effects on body weight only in the LNAME model (Figure 1D), whereas amlodipine significantly protected the DOCA hypertensive animals from body weight loss (Figure 1B).

Figure 2 demonstrates the effects of SAR407899 (3 mg/kg and 10 mg/kg), ramipril (1 mg/kg) and amlodipine (3 mg/kg) on blood pressure in the DOCA- (Figure 2A) and LNAME-treated rats (Figure 2B). SAR407899 effectively reduced blood pressure in both hypertensive models. Because the DOCA-induced hypertensive model is characterized by hypervolemia and resistance to ACE-inhibition, it was not surprising that ramipril had no significant effect on blood pressure. At the dose employed, amlodipine non-significantly lowered blood pressure in the DOCA rats. In the LNAME rats, all treatments significantly lowered blood pressure. In comparison to amlodipine and ramipril, SAR407899 showed superior blood pressure lowering effects at both doses in the LNAME rats. Thus, only SAR407899 was able to control blood pressure efficiently in both models and was therefore superior to the reference substances.

Kidney function (Figure 2C and D) was assessed by the measurement of albuminuria. In both models, SAR407899 dose-dependently reduced albuminuria. Ramipril significantly reduced albuminuria in only the LNAME model but not in the DOCA model. At the dose administered, amlodipine did not significantly reduce albuminuria in the DOCA or LNAME models. The lack of efficacy of amlodipine has been linked to the inability of CCB's to dilate renal efferent vessels, which is critical for improvement of the renal microcirculation.

Long term treatment effects of SAR407899 on heart and endothelial function

Figure 3 illustrates the effect of SAR407899 and of reference substances on heart function (A and B), measured in isolated Langendorff perfused hearts in the working heart mode and on vessel function *in vitro* (C and D). Hearts of hypertensive the DOCA rats and the LNAME rats were functionally compromised. At an afterload pressure of 40 mmHg (basal afterload), a similar heart performance was found in all groups; however, at higher afterload pressures (60 and 80 mmHg), a significant reduction was found in heart function from the DOCA- and LNAME-treated rats. Long-term treatment with SAR407899 restored heart function in both groups. In contrast, treatment with either amlodipine or ramipril had no significant effect. Endothelial function was found to be severely compromised in the DOCA rats. Figure 3C and D show the effect of SAR407899 and the reference substances on endothelial function. Long-term treatment with SAR407899 improved endothelial function in a dose-dependent manner (Figure 3C). As expected, ramipril had no effect on endothelial function of arteries from the DOCA-induced hypertensive rats (Figure 3D). Amlodipine had similar protective effects

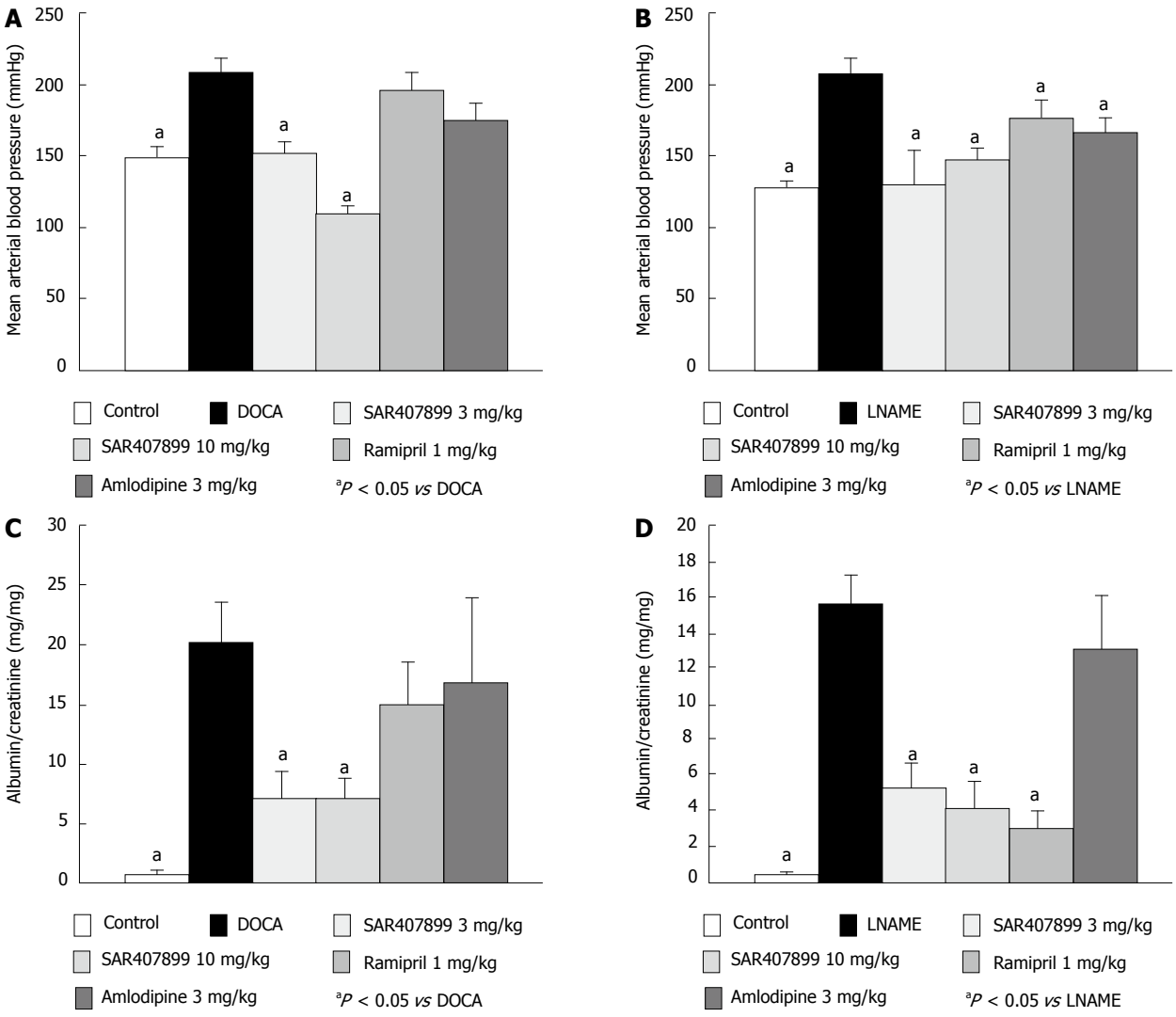

Figure 2 SAR407899 efficiently lowers blood pressure, proteinuria and mortality in hypertensive rats. Invasive measurement of blood pressure in deoxycorticosterone acetate (DOCA) (A) and in Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME) (B) rats. At the given dose, SAR407899 showed superior blood pressure lowering effect in comparison to ramipril and amlodipine in both animal models; C and D: Assessment of kidney function in DOCA and LNAME rats. SAR407899 showed significant protective effects on the kidneys in both models, whereas ramipril reduced albuminuria only in the LNAME model. Amlodipine had no therapeutic effect on kidney in either model.

on endothelial function in the DOCA hypertensive rats (Figure 3D). The endothelial function of arteries of the LNAME-treated rats has not been assessed because LNAME exerts a potent and long lasting inhibition of the endothelial nitric oxide synthase.

Effect of SAR407899 on DOCA- and LNAME-induced heart and renal pathology

Histological examination of the hearts of the DOCA- (Figure 4A-F) and LNAME-treated (Figure 4G-L) rats revealed a prominent perivascular fibrosis, massive infiltration of leukocytes into the interstitium and sclerotic changes. Figure 4A-C and 4G-I shows sirius red staining of DOCA- (Figure 4B) and LNAME-(Figure 4H) induced heart fibrosis in comparison to control (Figure 4A and G) and SAR407899 treatment (Figure 4C and I). Figure 4D-F and 4J-L shows haematoxylin eosin staining of DOCA- (Figure 4E) and LNAME-(Figure 4K) induced heart fibrosis in comparison to control (Figure 4D and J) and SAR407899 treatment (Figure 4F and L). In the hearts of the DOCA and LNAME rats, SAR407899 treatment at 10 mg/kg abolished the development of fibrosis (protection with SAR407899 at 3 mg/kg was less pronounced and data not shown). Chronic treatment of the LNAME hypertensive rats with SAR407899 attenuated leukocyte infiltration and perivascular fibrosis. Figure 4M and N summarize heart lesions according to the scoring procedure. The heart lesions of the DOCA rats were significantly reduced by SAR407899 at 10 mg/kg. Both reference compounds showed only marginal non-significant effects on heart lesions (Figure 4M). SAR407899 (at 3 and 10 mg/kg) and ramipril significantly diminished heart lesions in the LNAME-treated rats (Figure 4N). Histological analysis of kidneys from the DOCA- (Figure 5A-F) and LNAME- (Figure 5G-L) treated rats revealed severe

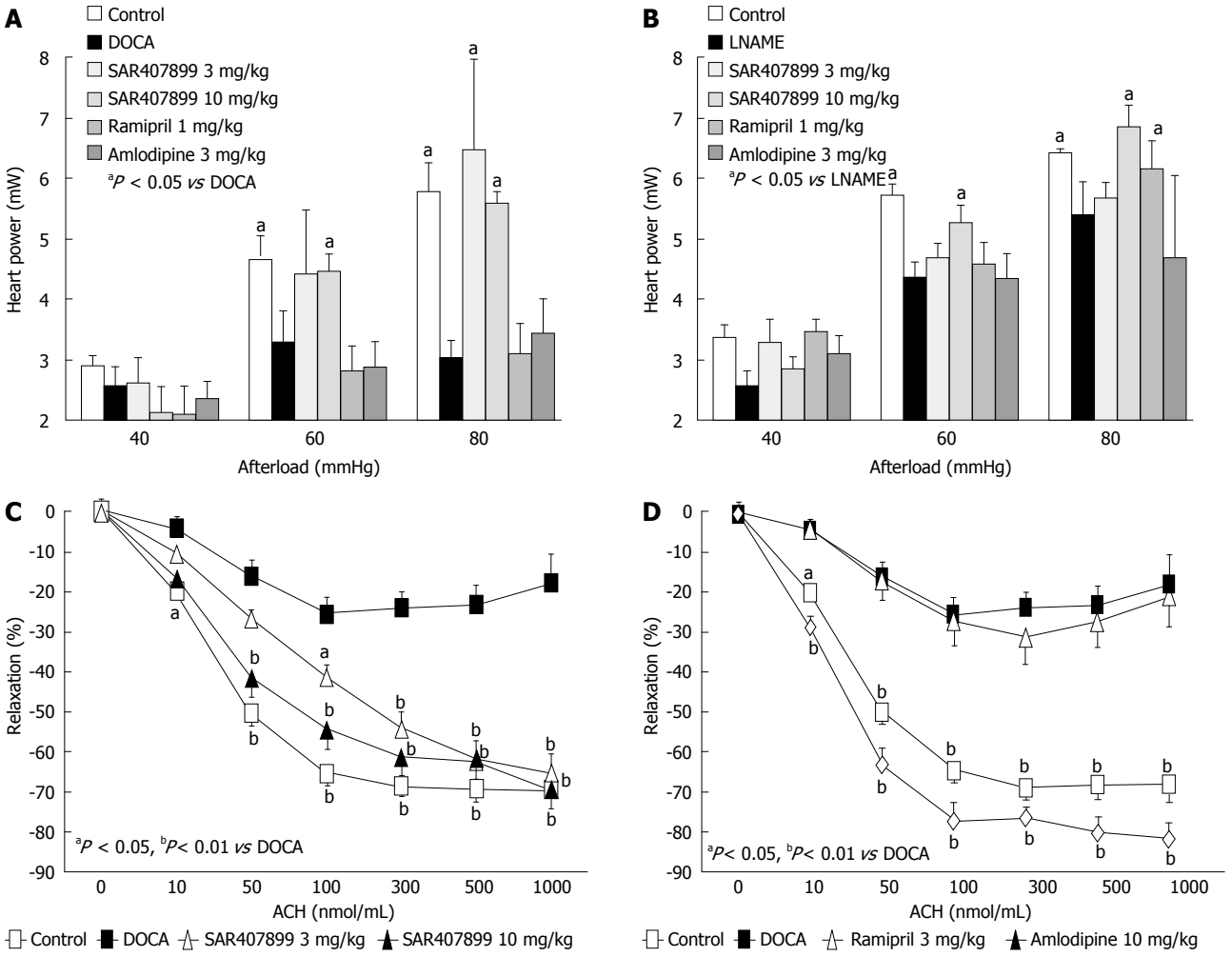

Figure 3 Effect of SAR407899 on heart and endothelial function. Measurement of heart function of isolated hearts of deoxycorticosterone acetate (DOCA) (A) and Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME)-treated rats (B). SAR407899 showed a significant improvement of heart function compared to reference substances at both doses and in both models; C and D: Measurement of endothelial function of aortas of DOCA rats treated with SAR407899 (C) or with reference substances (D). Ramipril treatment had no effect on endothelial function. Long-term treatment with SAR407899 improved endothelial function in a dose-dependent fashion. Amlodipine had similar protective effects as SAR407899.

lesions of glomeruli and tubuli. Figure 5A-C shows haematoxylin eosin staining in kidneys of DOCA- and of LNAME-treated rats (Figure 5G-I). Figure 5D-F shows podocin staining in kidneys of DOCA- and of LNAME-treated rats (Figure 5J-L). In kidneys from the DOCA rats (Figure 5B), severe destruction and sclerotic changes of glomeruli were associated with fibrinous discharges into the capsule, swelling of lobuli and multiple fibrotic events. In comparison to control (Figure 5A), a strong hypertrophy of glomeruli was detectable in the kidneys of the DOCA- treated animals (Figure 5B). Podocin staining (Figure 5D-F)of the DOCA rat kidneys revealed a drastic loss of podocin positive cells (podocytes) upon DOCA treatment (Figure 5E) in comparison to control (Figure 5D). Chronic treatment with SAR407899 attenuated these glomerular (much stronger staining of podocytes), vascular, and interstitial changes (Figure 5F). In contrast to kidneys of control animals (Figure 5G), in the kidneys from the LNAME hypertensive animals (Figure 5H), many changes were detected, including fibrotic changes, infiltration of leukocytes, hypertrophy of glomeruli, marked thickening and inflammation of the vascular wall, hyperplasia and degeneration of tubuli, and tubulointerstitial changes with inflammatory cell infiltration. Again, chronic treatment with SAR407899 attenuated these pathophysiological changes (Figure 5I).

Figure 5K shows the fading of podocin staining upon LNAME treatment indicating that podocin positive cells are damaged. Figure 5J demonstrates podocin staining in control animals. Long-term treatment with SAR407899 attenuated glomerular, vascular, and interstitial changes (Figure 5L). Figure 5M and N summarize kidney lesions according to the scoring procedure. The kidney lesions of the DOCA rats were significantly reduced by SAR407899 at 3 and 10 mg/ kg. Both reference compounds showed only marginal non-significant effects on kidney lesions (Figure 5M). SAR407899 (at 3 and 10 mg/kg) and ramipril significantly diminished kidney lesions in the LNAME-treated rats (Figure 5N). Expression of genes characteristic of fibrosis and leukocyte infiltration of the kidneys of the DOCA- and LNAME-treated rats was measured using RT PCR (Figure 6A-F). The expression of collagen

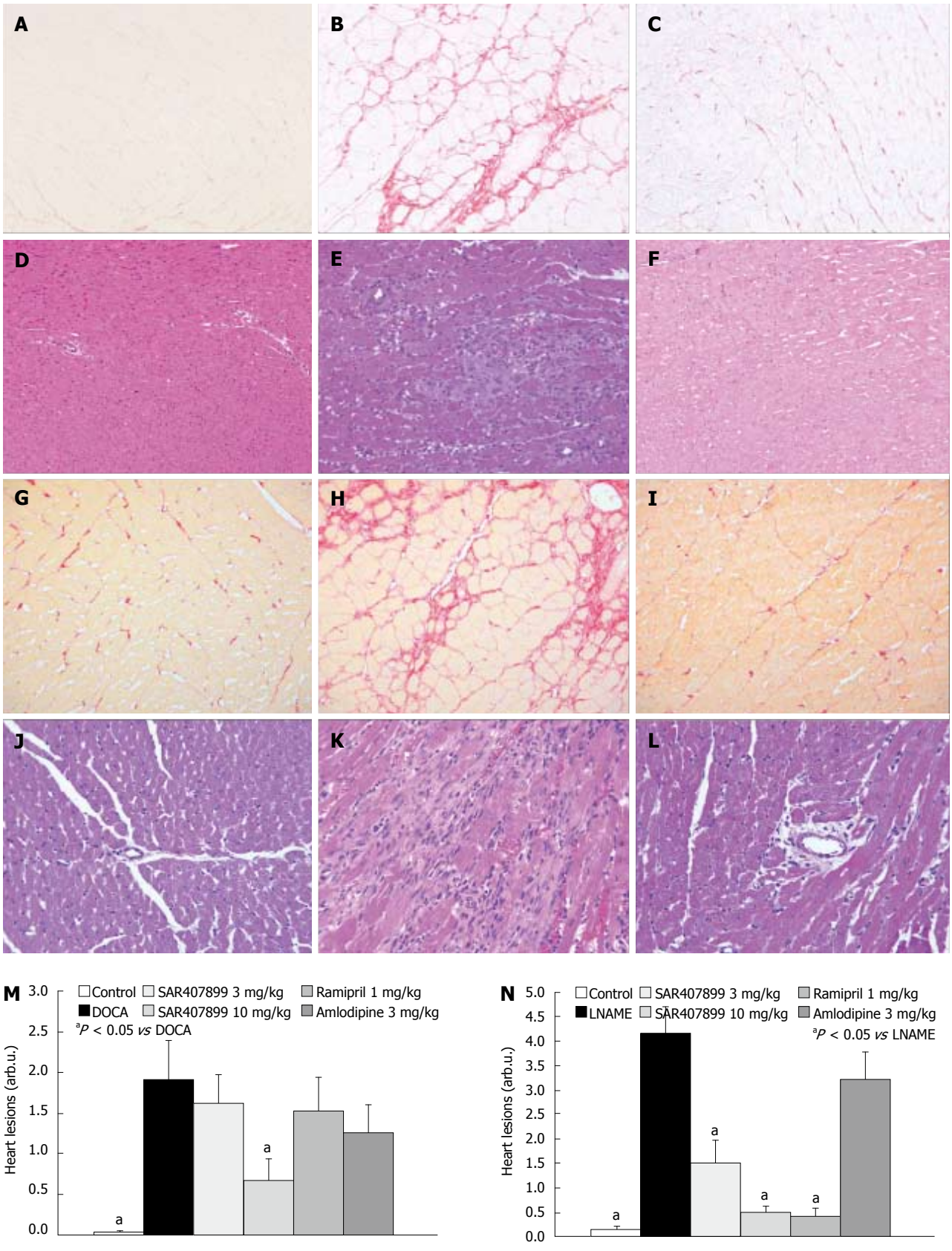

Figure 4 Histological examination of the effect of SAR407899 on the heart. Sirius red staining of hearts of deoxycorticosterone acetate (DOCA) (A-C) and Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME) rats (G-I) showed a strong induction of myocardial fibrosis. Upon treatment with SAR407899 at 10 mg/kg, significant protective effects were observed. Haematoxylin eosin staining of hearts of DOCA (D-F) and LNAME rats (J-L) showed perivascular fibrosis, massive infiltration of leukocytes into the interstitium and sclerotic changes. SAR407899 treatment at 10 mg/kg attenuated multifocal fibrosis, perivascular fibrosis and leukocyte infiltration. M and N: Summary of heart lesions and the effect of SAR407899 and reference substances in DOCA (M) and LNAME rats (N). A, D, G, J: Control; B, E: DOCA; H, K: LNAME; C, F, I, L: SAR407899 10 mg/kg.

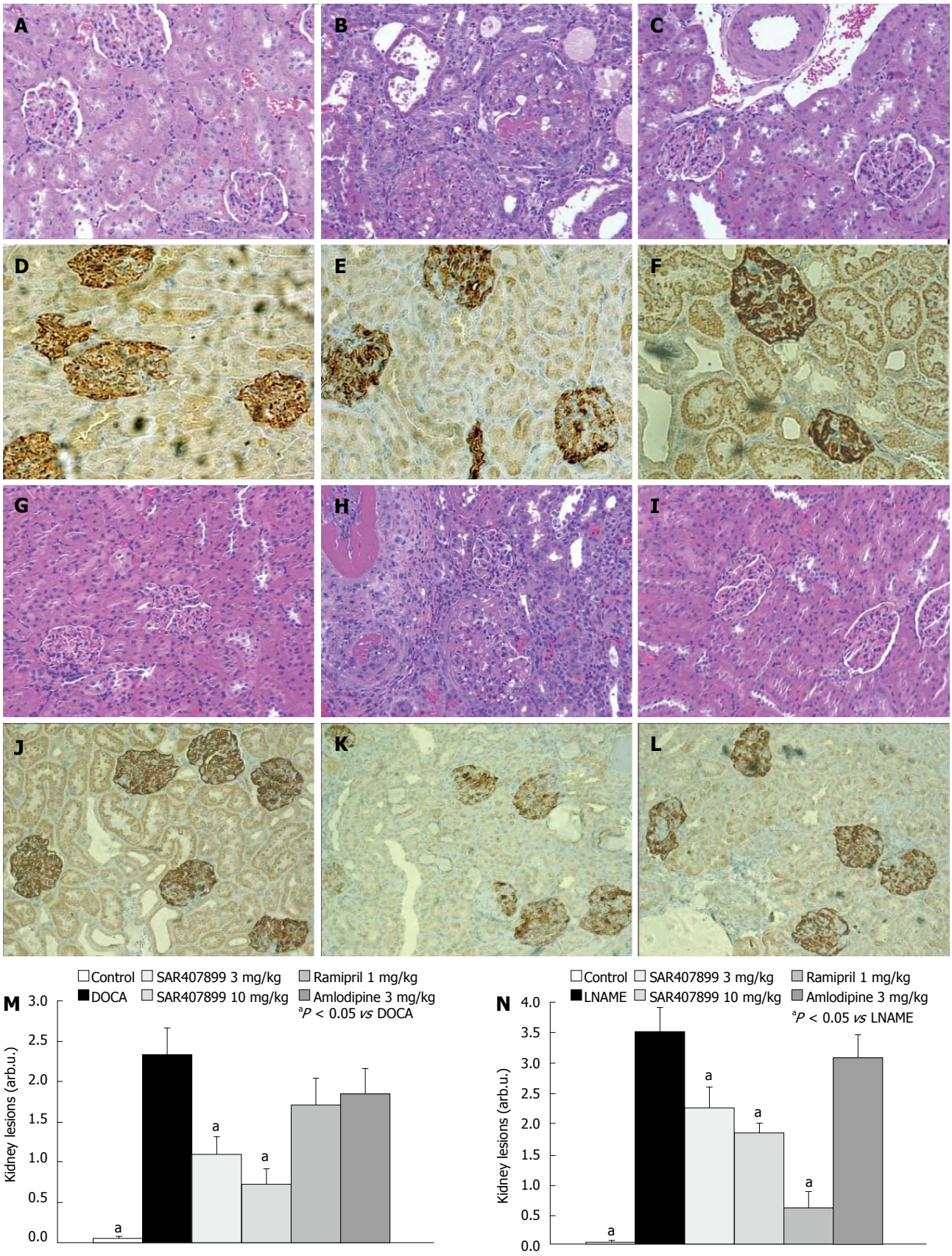

Figure 5 Histological examination of the effect of SAR407899 on the kidney. A-C: Haematoxylin eosin staining of normal glomeruli in control rats (left), sclerotic changes, dilation and hypertrophy of glomeruli of deoxycorticosterone acetate (DOCA) rats (center) and protective effects of SAR407899 at 10 mg/kg (right); D-F: Podocin staining in kidneys. Upon DOCA treatment, massive loss of podocytes can be detected. SAR407899 at 10 mg/kg exerts a protective effect in the kidneys of DOCA rats and rescues podocytes; G-I: Haematoxylin eosin staining of normal glomeruli in control rats (left), severe fibrotic changes, infiltration of leukocytes, and hypertrophy of glomeruli of Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME) rats (center), protective effects of SAR407899 at 10 mg/kg (right); J-L: Loss of podocytes upon LNAME treatment. SAR407899 at 10 mg/kg protected against loss of podocytes. Summary of kidney lesions and effect of SAR407899 and reference substances in DOCA (M) and LNAME rats (N). A, D, G, J: Control; B, E: DOCA; H, K: LNAME; C, F, I, L: SAR407899 10 mg/kg.

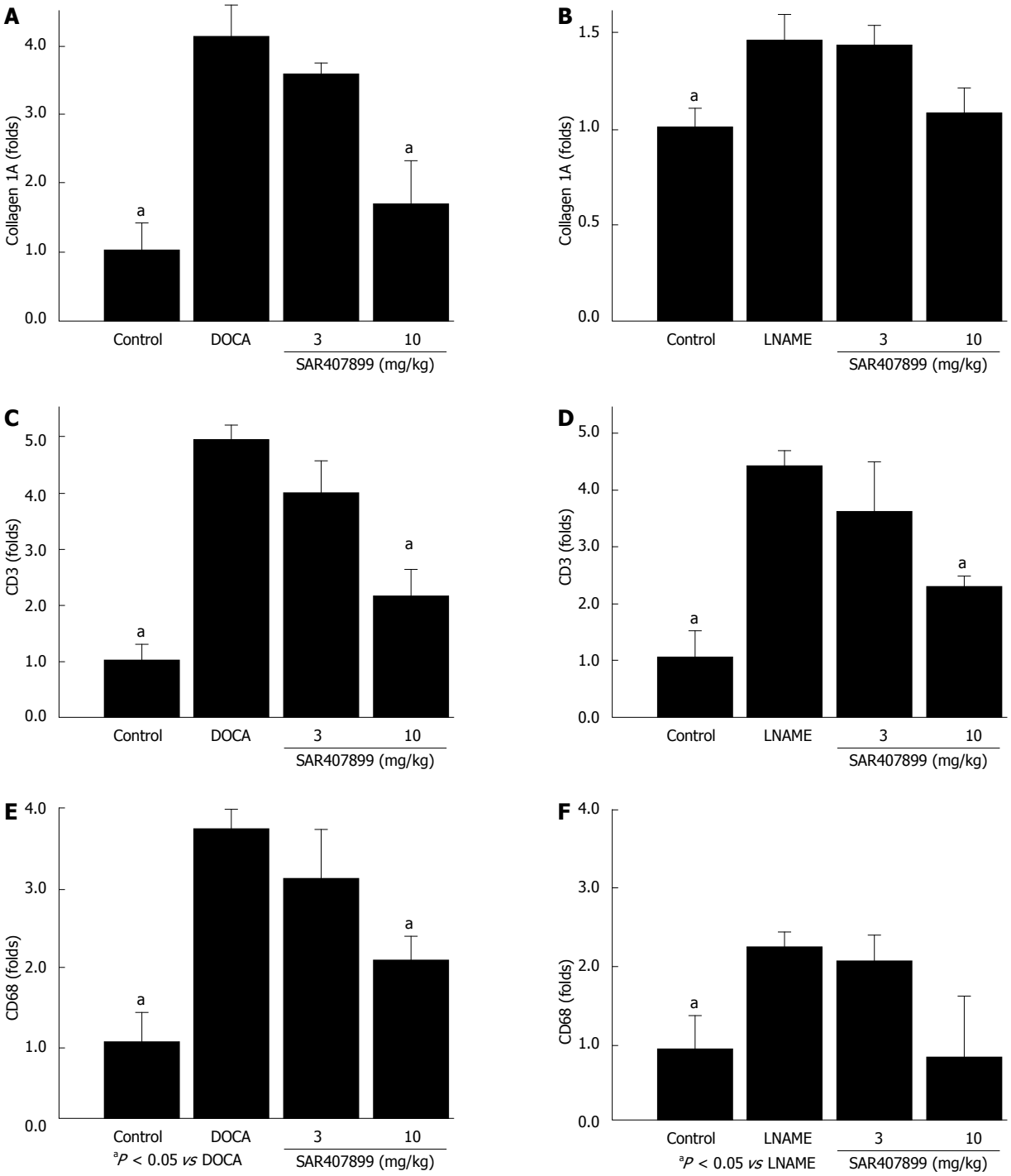

Figure 6 Effect of SAR407899 on the expression of fibrotic and leukocyte genes in the kidney. Determination of collagen, T cell (CD3) and macrophage (CD68) expression in the kidneys of deoxycorticosterone acetate (DOCA) (A, C and E) and Nω-Nitro-L-arginine methyl ester hydrochloride (LNAME) (B, D and F) rats. Expression of collagen was significantly increased upon DOCA and LNAME treatment. Upon DOCA or LNAME treatment, CD3 and CD68 abundance was induced, indicating that leukocytes infiltrated into the kidneys. SAR407899 treatment reduced expression of collagen and leukocyte genes in both models.

was significantly increased upon DOCA and LNAME treatment. SAR407899 at 10 mg/kg significantly reduced collagen expression in the kidneys of the DOCA rats and non-significantly in the kidneys of the LNAME rats (Figure 6A and B). Leukocyte infiltration into kidney tissue was quantified by measuring CD3 (T lymphocytes) and CD68 (macrophages) mRNA abundance in the kidneys of the DOCA and LNAME rats. Upon DOCA or LNAME treatment, both parameters were significantly induced, thus indicating significant leukocyte infiltration. SAR407899 at 10 mg/kg efficiently reduced leukocyte infiltration in the kidneys of the DOCA rats and non-significantly in the kidneys of the LNAME rats (Figure 6E and F), presumably by inhibition of leukocyte migration.

DISCUSSION

It has been generally accepted that RhoA-associated

kinases (ROCK1 and ROCK2) have important functions not only in vascular smooth muscle contractility but also in actin cytoskeleton rearrangement, cell adhesion, cytokinesis and motility in various cell types[7-12,27-31]. Two commercially available ROCK-inhibitors, fasudil and Y27632 were used in the majority of the published *in vitro* and *in vivo* studies. Both compounds were identified in the mid-1980s and were used to elucidate the pathophysiological role of ROCKs in several pathologies. Y27632 was first claimed in a patent in 1988[32,33] as a calcium channel blocker, and fasudil was patented in 1986[34,35], also as a novel calcium channel blocker. Later, discovery of ROCKs[36] led to the identification of these kinases as a direct target of both compounds. However, fasudil and Y27632 possess some unfavorable properties, including limited selectivity and importantly, a short duration of action. The latter might be a reason why fasudil was often administered at high doses, *e.g.*, 30 mg/kg per day or 100 mg/kg per day[37] in *in vivo* animal studies, which increases the probability of non-specific and toxic effects in different organs. In long-term animal studies of hypertension in which fasudil was used at low doses, *e.g.*, 10 mg/kg, no significant blood pressure lowering effect and only a partial renoprotective effect were found[38,39].

SAR407899 is a selective and potent inhibitor of ROCK that has been extensively characterized *in vitro*[21]. Acute treatment of conscious hypertensive animals (SHR, SHR-sp, LNAME or DOCA-salt treated rats) with SAR407899 resulted in a strong and sustained fall in blood pressure[21]. To evaluate the long-term effects of SAR407899, the compound was tested in two models of hypertension, one non-sensitive (DOCA) and the other sensitive (LNAME) to ACE-inhibition. The treatment effects of SAR407899 were compared to two current standard medications for high blood pressure, namely the inhibition of ACE (ramipril) or calcium channels blockade (amlodipine). As expected, treatment with ramipril demonstrated potent blood pressure lowering and end organ protective effects in the LNAME but not in the DOCA hypertension model[24,40,41]. Because the DOCA hypertensive model is characterized by hypervolemia and low plasma renin levels, this model is insensitive to ACE-inhibition[23]. The treatment effects of amlodipine at the given dose were small and non-significant in both models. Our data are in good agreement with several other studies in which amlodipine was found to be ineffective in protecting kidney function and structure in the DOCA rat or less effective than ACE-inhibitors in the LNAME rat[22,42,43]. Even when amlodipine was dosed three times higher, *e.g.*, at 10 mg/kg, no reduction in proteinuria or glomerular damage was found in the DOCA rats, although amlodipine efficiently lowered blood pressure. However, in other models, *e.g.*, in the LNAME rats, treatment with amlodipine showed pronounced protective effects on end organ damage and myocardial protection combined with the efficient blood pressure lowering effect in different rat strains. The lack of efficacy of amlodipine has been further linked to the inability of CCBs to dilate renal efferent vessels to improve renal microcirculation[22,43-47]. Long-term treatment with SAR407899 showed an efficient dose-dependent blood pressure reduction in both models with no signs of tachyphylaxia over the course of 35 d. Blood pressure lowering effects and protective effects on hypertension related end organ damage of SAR407899 were superior to ramipril and amlodipine in the DOCA rat. Typical end-organ damage observed upon chronic LNAME administration (hypertrophy and fibrosis of the heart, fibrosis of the kidney, glomerulosclerosis, tubular degeneration and leukocyte-infiltration) was significantly reduced in the SAR407899-treated animals as supported by histopathological and gene expression analyses. Albuminuria, which is considered the key parameter of kidney damage in general and of glomerular damage in particular, were strongly induced in the DOCA- and LNAME-challenged rats. Chronic administration of SAR407899 significantly reduced albuminuria in both models. Histologically visible improvements should translate into functional benefits (endothelial function and heart contractility) observed upon SAR407899 administration. Indeed, hearts of hypertensive the DOCA or LNAME animals treated with SAR407899 showed a significantly improved heart function (measured as heart power *in vitro*). Moreover, endothelial-dependent relaxation (*in vitro*) was significantly and dose-dependently improved after long-term treatment with SAR407899. Histological scoring and quantitative real time PCR analysis revealed a significant reduction in interstitial fibrosis, as measured by sirius red staining and collagen expression, respectively. SAR407899 treatment significantly reduced tissue expression of CD3 and CD68 (markers of infiltrating leukocytes and macrophages) in both models, which can be explained by the role of ROCKs in cellular migration and cytokinesis through modulation of the cytoskeleton. Similar data were reported by several groups studying the effect of ROCK inhibition on macrophage migration in atherosclerotic plaques[48-50]. Therefore, the beneficial effects of SAR407899 do not depend on only blood pressure control but also the suppression of inflammatory and fibrotic events in the target organs. These data suggest that inhibition of ROCKs could bring clear therapeutic benefit through different mechanisms and is not limited to vasorelaxation only. Recently, other authors stated that potential benefits of ROCK-inhibition, direct or indirect, could be more far-reaching than first thought[13]. Further studies using highly selective, potent, and safe ROCK inhibitors could open new perspectives for ROCK-based therapies in several different clinical indications.

COMMENTS

Background

Large clinical trials have demonstrated that current treatment with angiotensin converting enzyme-inhibitors, Angiotensinreceptor-blockers or calcium channel blockers only modestly reduces the progression of chronic kidney diseases. Hypertension increases the risk of target organ damage, including heart hypertrophy, heart ischemia, kidney dysfunction or failure, cerebrovascular events and malfunction of the endothelial tissue.

Research frontiers

Rho-kinase (ROCK) is considered an important target for a variety of cardiovascular diseases, including hypertension and hypertension-related end-organ damage. Several inhibitors of ROCK have been extensively used to evaluate the role of ROCK in cardiovascular physiology and pathology. However, these inhibitors have a moderate specificity, moderate potency and short duration of action *in vivo* that limit their clinical use. Therefore, the development of a more potent and specific inhibitor with a better pharmacokinetic profile is needed to explore the potential of ROCK inhibition in the therapy of hypertension and its complications.

Innovations and breakthroughs

The authors have identified a novel, potent and selective inhibitor of ROCK (SAR407899) and characterized its long-term effects in two animal models of hypertension.

Applications

ROCK-inhibition by the SAR407899 represents a new therapeutic option for the treatment of hypertension and its complications.

Terminology

Rho-kinases (ROCK1 and ROCK2) are intimately involved in the transmission of contractile signaling within smooth muscle tissue. Upon activation of the small GTPase RhoA by ligand-bound specific GPCRs, ROCKs, the downstream effectors of RhoA, phosphorylate the myosin light chain phosphatase and the myosin regulatory light-chain itself, resulting in a net increase in activated myosin. This promotes smooth muscle contraction and actin cytoskeleton re-organization. Inhibition of ROCKs leads to relaxation of vascular smooth muscle cells and, consequently, to a decrease in blood pressure.

Peer review

This article is particular meaningful for hypertension-related end-organ damage.

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DOI: 10.4330/wjc.v7.i1.43

World J Cardiol 2015 January 26; 7(1): 43-46
ISSN 1949-8462 (online)
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CASE REPORT

Permanent transvenous pacemaker implantation in a patient with Cor triatriatum dextrum

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Author contributions: Xiang K, Moukarbel GV and Grubb B designed and wrote the report; Xiang K and Moukarbel GV performed the transesophageal echocardiogram; Xiang K and Grubb B performed the dual-chamber pacemaker placement.

Ethics approval: This is a clinical case report. All patients related identification information have been avoided according to the policy of University of Toledo Medical Center and the Health Insurance Portability and Accountability Act (HIPPA) by the United State of America.

Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest: All authors have no conflict-of-interest to disclose.

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Received: August 17, 2014
Peer-review started: August 20, 2014
First decision: November 19, 2014
Revised: December 3, 2014
Accepted: December 18, 2014
Article in press: January 4, 2015
Published online: January 26, 2015

Abstract

Cor triatriatum dextrum is an extremely rare congenital heart abnormality in which the right atrium is separated into two chambers by a persistent fibrous membrane. A transvenous approach to place a dual-chamber pacemaker in such patients is technically challenging. We report the first case of a transvenous permanent pacemaker placement in a patient with cor triatriatum dextrum. An 87-year-old woman was diagnosed with paroxysmal atrial fibrillation. She was accidentally found to have cor triatriatum dextrum during the transesophageal echocardiography (TEE) prior to cardioversion. Later during her hospital stay, it was indicated to place a permanant pacemaker due to high grade atrioventricular block. After thorough reviewing TEE imagings, a transvenous catheter-based approach was decided feasible. Patient successfully received a dual chamber pacemaker through left subclavian venous approach. Furthermore in our case, using specially designed pacemaker leads and cautious intra-procedural maneuvering under fluoroscopic guidance ensured procedural success. In summary, a thorough pre-operative evaluation with transesophageal echocardiography is critical for the planning and eventual success of the transvenous placement of right-sided leads.

Key words: Congenital heart defect; Complete heart block; Inter-atrial membrane; Dual-chamber pacemaker

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Core tip: Cor triatriatum dextrum is an extremely rare congenital heart abnormality in which the right atrium is separated by a persistent fibrous membrane. This membrane poses a technical challenge for dual-chamber pacemaker placement through the transvenous approach. Here we report the first transvenous pacemaker placement in a patient with cor triatriatum dextrum. A thorough pre-operative evaluation by transesophageal echocardiogram was critical for the planning of transvenous catheter-based right-sided leads placement. Using specially designed pacemaker leads and cautious

intra-procedural maneuvering under fluoroscopic guidance ensured procedural success.

Xiang K, Moukarbel GV, Grubb B. Permanent transvenous pacemaker implantation in a patient with Cor triatriatum dextrum. *World J Cardiol* 2015; 7(1): 43-46 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i1/43.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i1.43

INTRODUCTION

Cardiovascular disease is the leading cause of mortality and mobility according to recent statistics[1]. Adult congenital heart disease has become an important entity in the current cardiology practice due to the advances in pediatric cardiac care and improved survival[2]. Commonly seen congenital heart conditions include septal and valvular defects. Cor triatriatum dextrum is an extremely rare congenital heart anomaly in which the right atrium is separated into two chambers by the persistence of the right sinus venosus valve[3]. It is uncommon to encounter such patients requiring placement of a permanent pacemaker. We report the placement of a dual-chamber pacemaker through the transvenous approach in a patient with cor triatriatum dextrum. To our knowledge, there are no similar reports in the published literature.

CASE REPORT

An 87-year-old woman presented to the hospital with complaints of dyspnea on exertion. She has no significant medical history other than prior cigarette smoking. On her arrival to the emergency room she was found to be in atrial fibrillation with rapid ventricular response. She was treated with heart rate control medications and anticoagulation. A transesophageal echocardiogram (TEE) was performed prior to cardioversion to normal sinus rhythm given poor rate control. This revealed the presence of a well-defined transverse membrane dividing the right atrium (Figure 1) consistent with the diagnosis of cor triatriatum dextrum. Color Doppler evaluation indicated separation of blood flow in the two divisions of the right atrium. However the division of the right atrium by this membrane was not complete. Color Doppler confirmed partial obstruction in the superior portion (Figure 2). The right atrium was enlarged without significant tricuspid regurgitation. An enlarged coronary sinus was noted with a measured diameter of 15.8 mm. Agitated saline injections *via* the left arm showed no saline contrast in the coronary sinus, indicating the absence of a persistent left superior vena cava. In addition, a small atrial septal defect (ASD) (measured diameter 3 mm) with a left to right shunt was demonstrated by color flow Doppler (Figure 3). No thrombus was noted in the left atrium and left atrial appendage. Subsequently the patient was cardioverted to normal sinus rhythm without complication.

During her hospital course, she was found to have Morbitz type Ⅱ AV block along with periods of complete heart block by remote cardiac monitoring station. Considering patient's daily functional capacity predicting reasonable life expectancy, the decision was made to implant a permanent dual-chamber pacemaker. The presence of cor triatriatum dextrum with a membrane partially obstructing the cavity of the right atrium, presented a technical challenge in regards to adequate placement of the right ventricular and right atrial leads *via* the transvenous approach. After obtaining left subclavian venous access, a 6-French St. Jude Medical pacing electrode was inserted *via* a breakaway introducer sheath. The lead was gently guided to the area near the opening of the interatrial membrane. The area was gently probed with the pacing lead until it was seen to dip into the lower atrial area. Care was taken not to cross the ASD with the lead. Once the inner atrial membrane had been crossed, the lead was then advanced and fluoroscopically guided into the right ventricular apex. Once adequate positioning had been determined, the active fixation coil was deployed. *Via* a second breakaway introducer sheath, a Boston Scientific Dextrus active fixation lead was fluoroscopically guided into an area just below the membrane within the right atrial appendage, and the active fixation coil deployed (Figure 4). Each lead was then connected to a Boston Scientific Ingenio dual-chamber pulse generator. *Via* off field telemetry, adequate sensing and pacing levels of the leads were determined. The patient was discharged to home the next day.

DISCUSSION

The prevalence of adult congenital heart disease has increased in the past 10 years and its management has proposed new challenges to current cardiology practice[2]. We presented a case of successful pacemaker lead placement in a patient with non-obstructive cor triatriatum dextrum. Cor triatriatum dextrum is an extremely rare congenital heart abnormality in which the right atrium is separated into two chambers by the persistence of the right sinus venosus valve[3]. The superior chamber receives the venous blood from both vena cava and the inferior chamber is in contact with the tricuspid valve and the right atrial appendage. The size of the communicating orifice between the superior and inferior atrial chambers determines the natural course of cor triatriatum dextrum. If the communicating orifice is small, the patient shows symptoms of congestive heart failure during infancy or childhood and usually requires surgical intervention for survival. If the connection is large and non-obstructive, patient may remain asymptomatic for many years, as in our case. The clinical presentation therefore is somewhat variable. Patients with cor triatriatum dextrum may present with recurrent supraventricular tachycardia, right-side heart failure, or cyanosis in the presence of ASD with right-to-left shunt. In our case, patient presented initially with atrial fibrillation with rapid ventricular response. The disorder can be treated surgically in symptomatic patients by

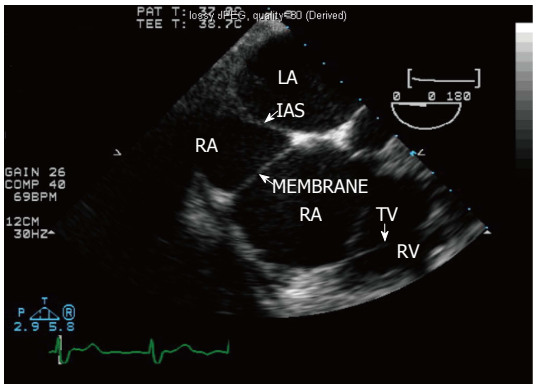

Figure 1 Four-chamber transesophageal echocardiogram view showing the division of the left atrium into two chambers by a transverse membrane. IAS: Interatrial septum; LA: Left atrium; RA: Right atrium; RV: Right ventricle; TV: Tricuspid valve.

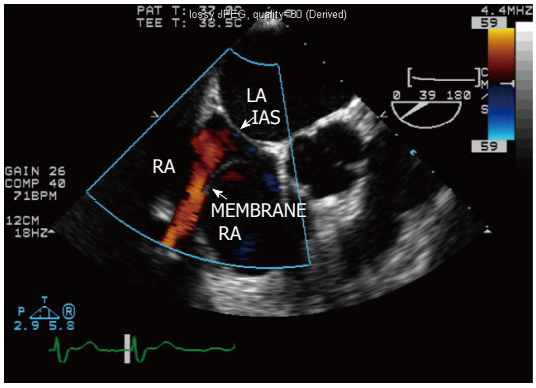

Figure 2 Color flow Doppler demonstrating the partially obstructive nature of the membrane, with blood flow through a small connection in the superior portion of the right atrium between the two chambers. IAS: Interatrial septum; LA: Left atrium; RA: Right atrium.

removing the membrane dividing the atrium.

During normal embryogenesis, the right atrium is formed by two different portions joining together: the right horn of the sinus venosus that forms the smooth posterior portion, and the original embryologic right atrium that forms the trabeculated anterior portion. The connection between these two portions is called sinoatrial orifice. The sinoatrial orifice is sided by two valvular folds that are called the right and left venous valves. During the development of right atrium, the right valve of the right horn of the sinus venosus forms a membranous valve that divides the right atrium in two parts. This valve directs oxygenated venous return from the inferior vena cava across the foramen ovale to the left side of the heart. This membranous valve normally regresses by the 12th week of gestation. Incomplete regression of the superior portion of right venosus valve forms membranes attached to the crista terminalis, while remnant of the inferior portion results in the Eustachian valve of the inferior vena cava, web-like remnant as Chiari network or the Thebesian valve of the coronary sinus. Failure of regression of this membrane causing persistent partition between the venous (smooth) and trabeculated portions of the right atrium

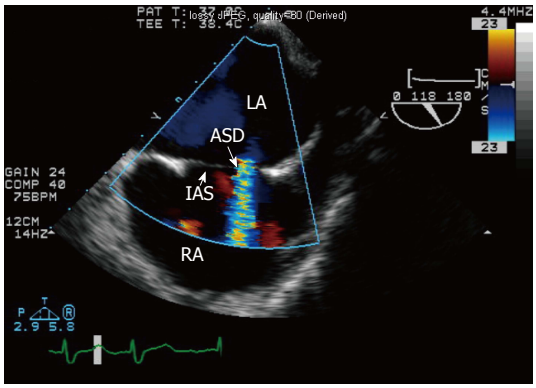

Figure 3 Color flow Doppler demonstrating a small atrial septal defect with left-to-right shunt. ASD: Atrial septal defect; IAS: Interatrial septum; LA: Left atrium; RA: Right atrium.

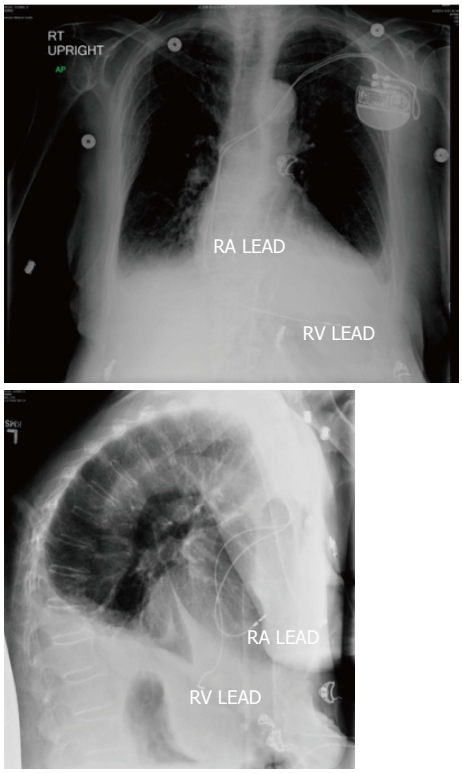

Figure 4 Chest X-ray showing proper placement of right ventricular and right atrial leads. RA: Right atrium; RV: Right ventricle.

leads to the formation of cor triatriatum dextrum[4].

Cor triatriatum dextrum has been associated with other congenital abnormalities, including ASD, patent foramen ovale, ventricular septal defect, hypoplastic right ventricle, hypoplastic tricuspid valve, and pulmonary atresia[3]. In our case, the presence of a small ASD posed the risk of crossing into the left atrium during manipulation of the lead across the atrial membrane. We also found an enlarged coronary sinus, measured diameter 15.8 mm (normal range 6.6 ± 1.5 mm)[5]. This is likely related to the elevated right atrial pressure. A rare but important congenital vascular anomaly associated with an enlarged coronary sinus is a persistent

left superior vena cava draining into the coronary sinus[6]. To investigate this possibility, an agitated saline injection *via* the left arm was performed during TEE and showed no saline contrast in the coronary sinus, indicating the absence of a persistent left superior vena cava.

Considering the rarity of cor triatriatum dextrum, a patient with such a congenital abnormality who requires a permanent pacemaker is unique. To our knowledge, this is the first reported case of a permanent pacemaker placement through a transvenous approach in a patient with cor triatriatum dextrum. Although it is technically challenging, transvenous catheter-based approach is feasible if the membrane in the right atrium is non-obstructive and caution exercised during the procedure. A thorough pre-operative evaluation by transesophageal echocardiogram was critical for the planning of the transvenous catheter-based right-sided leads placement. Using specially designed pacemaker leads and cautious intra-procedural maneuvering under fluoroscopic guidance ensured procedural success.

COMMENTS

Case characteristics

A 87-year-old woman presented with paroxysmal atrial fibrillation.

Clinical diagnosis

Atrial fibrillation with raid ventricular response, later was also diagnosed with high grade AV block.

Differential diagnosis

Any cause for atrial fibrillation and/or AV block such as hypertension, heart failure *etc*,.

Laboratory diagnosis

Lab test result was unremarkable.

Imaging diagnosis

A transesophageal echocardiogram revealed a rare congenital condition called cor triatriatum dextrum.

Treatment

A permanent pacemaker placement through a transvenous approach.

Related reports

To the knowledge, this is the first reported case of a permanent pacemaker placement through a transvenous approach in a patient with cor triatriatum dextrum.

Term explanation

Cor triatriatum dextrum is an extremely rare congenital heart abnormality in which the right atrium is separated into two chambers by the persistence of the right sinus venosus valve.

Experiences and lessons

Although it is technically challenging, transvenous catheter-based approach for a permanent pacemaker placement is feasible in a patient with cor triatriatum dextrum.

Peer review

It is interesting.

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P- Reviewer: Panduranga P, Santulli G **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
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