Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence

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Atrial fibrillation (AF) is a common arrhythmia that is difficult to treat. Anti-arrhythmic drug therapy, to maintain sinus-rhythm, is limited by inadequate efficacy and potentially serious adverse effects. There is increasing interest in novel therapeutic approaches that target AF-substrate development. Recent trials suggest that angiotensin converting-enzyme (ACE)-inhibitors and angiotensin-receptor blockers (ARBs) may be useful, particularly in patients with left ventricular hypertrophy or failure. The clinical potential and mechanisms of this approach are under active investigation. Angiotensin-II is involved in remodelling and may have direct electrophysiological actions. Experimental studies show protection from atrial structural and possibly electrical remodelling with ACE-inhibitors and ARBs, as well as potential effects on cardiac ion-channels. This article reviews information pertaining to the clinical use and mechanism of action of ACE-inhibitors and ARBs in AF. A lack of prospective randomized double-blind trials data limits their application in AF patients without another indication for their use, but studies under way may alter this in the near future. This exciting field of investigation may lead to significant improvements in therapeutic options for AF patients.

KEYWORDS
Arrhythmia; Atrial fibrillation; Renin–angiotensin-system; Drug therapy

Introduction

There is increasing recognition of down-stream effects of the renin–angiotensin–aldosterone system in atrial fibrillation (AF). Angiotensin-II is an octapeptide formed from the liver-derived 485-aminoacid precursor angiotensinogen (Figure 1). Angiotensinogen-gene polymorphisms are associated with increased non-familial AF1 and angiotensin converting-enzyme (ACE)-inhibitors or angiotensin-receptor blockers (ARBs) may prevent AF in some patients.

Angiotensin-II is important in the regulation of blood pressure, fibroblast proliferation, and cardiac hypertrophy (Figure 1). Angiotensin-II production is enhanced in congestive heart failure (CHF). Beneficial effects of ACE-inhibitors on mortality and morbidity in CHF patients were demonstrated in early clinical trials.2,3 ACE-inhibition also diminishes ventricular arrhythmias after myocardial infarction (MI).4–6 Both ventricular premature contraction numbers and the number of patients affected decline.6

A retrospective analysis of the SOLVD (Studies of Left Ventricular Dysfunction) trial suggested that ACE-inhibitors prevent AF in overt CHF.7 Other studies found protective effects of ACE-inhibitors against AF in patients with risk factors like arterial hypertension with left ventricular (LV) hypertrophy8 or acute MI with reduced left ventricular ejection fraction (LVEF).9 A recent meta-analysis suggested that renin–angiotensin system inhibition suppresses AF most clearly in patients with LV dysfunction.10

As previous reviews have summarized clinical evidence of anti-AF efficacy of ACE-inhibitors and ARBs, the present article updates clinical evidence and attempts to elucidate underlying mechanisms.

Methods

A PubMed literature search was performed with the keywords: AF, renin-angiotensin system, ACE-inhibitors, and ARBs. The search was constrained to articles with abstracts in English published between 2000 and 2005. Abstracts were reviewed for appropriateness. Reference lists of identified articles were reviewed for additional papers. Data were extracted from original papers published in peer-reviewed journals.

Clinical evidence

ACE-inhibitors reduce the incidence of new-onset AF

Table 1 summarizes clinical studies addressing ACE-inhibitor and ARB efficacy in AF.

A retrospective, longitudinal cohort study of 8 million cases compared AF incidence in hypertensive patients treated with ACE-inhibitors vs. calcium-channel blockers.11 A cohort of 10 926 patients (mean age ~65 years) was equally divided between groups. The adjusted hazards...
ratio for new-onset AF in the ACE-inhibitor group after 4.5-year average follow-up was 0.85 (95% confidence interval: 0.74–0.97). Several trials comparing ACE-inhibitors to other medications (beta-blockers, calcium-channel antagonists, and diuretics) in hypertensive patients found no significant difference. However, the LIFE trial (Losartan Intervention For Endpoint reduction in hypertension) showed significant reductions in AF occurrence for losartan- vs. atenolol-treated patients. ARBs reduced cardiovascular morbidity and mortality and stroke risk in hypertensive patients with previous AF. LIFE studied ARBs in patients with LV hypertrophy, whereas other trials assessed ACE-inhibitors in more general hypertensive populations.

AF is associated with impaired prognosis in post-MI patients. A retrospective study analysed ACE-inhibitor effects on AF occurrence in 1577 patients with sinus-rhythm and LVEF <35% post-MI. ACE-inhibition reduced AF occurrence by 55% vs. placebo (from 5.3 to 2.8%). The reduced AF incidence could not be explained by differences in serum K⁺-concentration or LVEF, supporting the primary role of ACE-inhibition.

In a SOLVD substudy including 391 patients with mean LVEF <30%, those receiving ACE-inhibitor treatment had reduced new-onset AF during a 2.9 ± 1.0-year follow-up (5.4 vs. 24% in placebo). ACE-inhibitors were more beneficial in the prevention arm (with preserved LVEF). Another retrospective analysis of SOLVD evaluated 192 hospitalizations for atrial tachyarrhythmias in 158 patients. ACE-inhibitor treatment was associated with reduced hospitalizations or death [relative risk (RR): 0.87, 95% confidence interval: 0.79–0.96, P < 0.007]. The hospitalization-rate with atrial tachyarrhythmias was also reduced (RR 0.64, 95% confidence interval: 0.48–0.85, P < 0.002). A post hoc analysis of Val-HeFT demonstrated that fewer patients with CHF and sinus-rhythm at baseline developed AF when receiving valsartan in addition to ACE-inhibitors (5.12 vs. 7.95%, P < 0.0002).

In summary, angiotensin-system inhibition appears to protect against AF in patients with hypertension and LV hypertrophy, post-MI with LV dysfunction, and chronic CHF. The effect is clearest in patients with LV systolic dysfunction.

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### Table 1. Clinical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Number of patients analysed</th>
<th>Study drug</th>
<th>Mean follow-up</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berg et al.</td>
<td>CHF + AF</td>
<td>18</td>
<td>Lisinopril vs. placebo</td>
<td>12 weeks</td>
<td>More patients in SR 6-weeks post-CV (34 vs. 71%, P = 0.16)</td>
</tr>
<tr>
<td>Vermes et al.</td>
<td>CHF</td>
<td>391</td>
<td>Enalapril vs. placebo</td>
<td>2.9 ± 1.0 years</td>
<td>Reduced new-onset AF (5.4 vs. 24%, P &lt; 0.0001)</td>
</tr>
<tr>
<td>Maggioni et al.</td>
<td>AF</td>
<td>4359</td>
<td>Valsartan vs. placebo</td>
<td>2.2 months</td>
<td>Lower AF incidence (17.9 vs. 18.9/1000 patient-years, P = 0.018)</td>
</tr>
<tr>
<td>Poletti et al.</td>
<td>AF</td>
<td>177</td>
<td>Trandolapril vs. placebo</td>
<td>4–5 years</td>
<td>Reduced new-onset AF (2.8 vs. 5.3%, P = 0.05)</td>
</tr>
<tr>
<td>L'Allier et al.</td>
<td>AF</td>
<td>10926</td>
<td>ACE-inhibitors vs. Ca²⁺-antagonists</td>
<td>4.5 years</td>
<td>Reduced AF incidence (17.9 vs. 18.9/1000 patient-years, P = 0.018)</td>
</tr>
<tr>
<td>Hansson et al.</td>
<td>HTN</td>
<td>11018</td>
<td>Captopril vs. beta-blocker and/or diuretics</td>
<td>6.1 years</td>
<td>Reduced composite primary endpoint: cardiovasc. mortality, stroke, MI (22.9 vs. 36.2%, P = 0.009)</td>
</tr>
<tr>
<td>Pedersen et al.</td>
<td>HTN</td>
<td>33249</td>
<td>Losartan vs. atenolol</td>
<td>2.9 ± 1.0 years</td>
<td>Reduced new-onset AF (5.4 vs. 15.0%, P &lt; 0.007)</td>
</tr>
<tr>
<td>Madrid et al.</td>
<td>AF</td>
<td>154</td>
<td>Amio vs. amio + irbesartan</td>
<td>Median 254 days</td>
<td>Improved SR maintenance (57.3 vs. 74.3%, P = 0.021)</td>
</tr>
<tr>
<td>Ueng et al.</td>
<td>AF</td>
<td>125</td>
<td>Amio vs. amio + enalapril</td>
<td>Median 270 days</td>
<td>Improved SR maintenance (57.3 vs. 74.3%, P = 0.021)</td>
</tr>
</tbody>
</table>

HTN, hypertension; SR, sinus rhythm; CV, cardioversion.
and CHF.\textsuperscript{10} As AF incidence was not a pre-specified endpoint in these retrospective studies, results need to be confirmed in prospective clinical trials. In addition, renin-angiotensin system inhibition effects on AF occurrence in patients without another medical indication for angiotensin-inhibitor treatment like hypertension, post-MI LV dysfunction or CHF, have not been systematically tested. The ongoing ACTIVE trial has a study arm comparing irbesartan vs. placebo.\textsuperscript{17} Another ongoing trial is studying olmesartan in paroxysmal AF (ANTIPAF: Angiotensin-II Receptor Blocker in Paroxysmal Atrial Fibrillation Trial).

**ACE-inhibitors prevent AF relapse after electrical cardioversion**

ACE-inhibition produced favourable haemodynamic effects and improved peak oxygen-consumption in CHF associated with AF,\textsuperscript{18} with a trend towards better sinus-rhythm maintenance (71\%) vs. placebo (36\%, \(P = \text{n.s.}\)) post-cardioversion. Retrospective analysis of 732 patients randomized to rhythm-control within AFFIRM demonstrated fewer AF relapses in ACE-inhibitor treated patients with CHF.\textsuperscript{19} Madrid et al.\textsuperscript{20} prospectively studied the effects of adding irbesartan to amiodarone-treatment after electrical cardioversion. AF recurrences were reduced in irbesartan-receiving patients. Similarly, Ueng et al.\textsuperscript{21} showed that adding an ACE-inhibitor to amiodarone reduced AF relapses post-cardioversion. In these trials, a combination of renin-angiotensin system inhibition with efficient anti-arrhythmic therapy led to further improved outcome in terms of freedom from arrhythmia relapse, albeit over a relatively short time-frame. A third trial demonstrated abbreviated signal-averaged P-wave duration, reflecting improved atrial conduction, after cardioversion in patients on long-term (6–12 months) ACE-inhibitor treatment.\textsuperscript{22}

**Experimental evidence**

**Potential mechanisms for benefits against AF**

Three mechanisms have been suggested to explain anti-arrhythmic actions of ACE-inhibitors and ARBs in AF (Figure 2):

(i) improved LV-haemodynamics and reduced atrial stretch;

(ii) suppressed angiotensin-II-induced fibrosis;

(iii) direct modulation of ion-channel function.

**ACE-inhibitors reduce atrial stretch**

Haemodynamic effects of ACE-inhibitors include systemic-arteriolar dilatation and increased large-artery compliance that decrease systolic blood pressure. In CHF, renin-angiotensin system inhibition reduces afterload and systolic wall-stress, improving cardiac function.\textsuperscript{23} ACE-inhibition also decreases left-atrial pressure and wall-stress.\textsuperscript{24} Acutely raised pressure increases atrial vulnerability by shortening refractory periods,\textsuperscript{25} possibly by opening stretch-activated channels.\textsuperscript{26} Atrial stretch following mitral-valve chordae tendineae rupture changes atrial electrophysiology (pronounced conduction slowing of premature beats), similar to experimental CHF-related AF.\textsuperscript{27,28} Experimental CHF includes a significant stretch component, as most CHF animals develop mitral regurgitation.\textsuperscript{28} Mitral regurgitation slows impulse propagation, promoting AF in dogs.\textsuperscript{29} Sheep subjected to aorto-pulmonary shunt-generation develop left-atrial dilatation and altered atrial electrophysiology (action-potential shortening; \(I_{Ca,L}\) reduction), along with predisposition to AF.\textsuperscript{30} Rabbits with chronic volume overload demonstrate re-entrant and focal left-atrial activity.\textsuperscript{31}

Stretch is not the only determinant of the AF substrate in CHF. AF can still be induced despite reversal of atrial dilatation after recovery from tachypacing-induced CHF.\textsuperscript{32} Mimicking the haemodynamic effects of ACE-inhibition does not suppress experimental CHF-related AF, whereas ACE-inhibition does, suggesting that haemodynamic effects are insufficient to account for ACE-inhibitor actions.\textsuperscript{33}

**Preventing fibrosis**

Angiotensin-II regulates cardiac-fibroblast proliferation.\textsuperscript{34} Transforming growth factor-\(\beta 1\) (TGF-\(\beta 1\)) may be particularly important for atrial fibrosis.\textsuperscript{35–37} Angiotensin-II binding to AT\(_1\) receptors stimulates fibrous-tissue formation by promoting TGF-\(\beta 1\) synthesis.\textsuperscript{35} Selective cardiac overexpression of TGF-\(\beta 1\) in transgenic mice causes atrial but not ventricular fibrosis, with predisposition to AF.\textsuperscript{36} There are greater local angiotensin-II levels in atria than ventricles of CHF dogs and atrial (but not ventricular) TGF-\(\beta 1\) is activated during the development of CHF.\textsuperscript{37} Cardiac-specific ACE overexpression produces atrial enlargement and AF,\textsuperscript{38} consistent with an angiotensin-II/fibrosis/AF link.

In experimental CHF, ACE-inhibitor treatment inhibits fibrosis and reduces AF duration.\textsuperscript{33} CHF-induced ion-current changes are reversible upon recovery from experimental CHF but atrial fibrosis persists, along with increased AF duration.\textsuperscript{33} However, ACE-inhibitor protection against fibrosis and AF promotion is incomplete, and some changes (cell death, inflammatory-cell infiltration, activation of mediators) are not prevented.\textsuperscript{39}

Increased atrial angiotensin-II concentrations precede plasma concentration rises in ventricular-tachypacing induced CHF,\textsuperscript{39} suggesting intracardiac angiotensin-II

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**Figure 2** Direct and indirect atrial actions of angiotensin-II. Angiotensin-II leads to LV hypertrophy and fibrosis. Abnormal relaxation increases L V-end-diastolic pressure, increasing atrial pressure and stretch, thereby favouring AF occurrence. Angiotensin-II enhances fibroblast activity and promotes fibrosis. Direct cellular electrophysiological effects may also contribute to AF. AF may also up-regulate local ACE. Grey arrows: secondary atrial effects mediated through venricular actions of angiotensin-II; black arrows: direct atrial effects.
formation. Local ACE-synthesis is increased in chronic human AF. In human right-atrial samples, AT1- and AT2-receptors may be differentially regulated in AF: AT1-receptors downregulated and AT2-receptors (with potential anti-proliferative actions) upregulated. In other studies, AT1 receptors were found to be upregulated in left and unchanged in right atria and experimental data demonstrated increased AT1- and AT2-receptor expression. Thus, angiotensin-receptor behaviour in AF modulate cardiac angiotensin-II effects by blocking AT1-receptors; however, there is no evidence to suggest AT2-receptors in the presence of unhindered stimulation of AT2-receptors; however, there is no evidence to suggest superiority of ARBs vs. ACE-inhibitors in AF.

There is evidence for a role of angiotensin-II in mediating inflammatory responses, which may additionally be involved in AF. Aldosterone-antagonism reduces ventricular fibrosis in hypertensive heart disease and might be useful in preventing atrial fibrosis.

**Anti-arrhythmic effects of ACE-inhibitors and ARBs**

ACE-inhibitors and ARBs prevented atrial electrophysiological changes during several hours of atrial tachycardia in dogs. However, although angiotensin-II infusion to patients increased blood pressure, there was no change in atrial ERP, ERP-dispersion, conduction properties, or AF inducibility. Enalapril does not affect atrial remodelling caused by 7-day atrial-tachypacing.

Sustained AF induced in dogs by 5-week atrial-tachypacing, with uncontrolled ventricular rates, caused LV-dysfunction. Candesartan (10 mg/kg/day), started a week before tachypacing-onset and continued throughout tachypacing, reduced AF duration. Atrial ERP-shortening was unaffected, indicating benefit independent of rate-dependent remodelling. Candesartan reduced interstitial fibrosis (7 ± 2 vs. 16 ± 1% in controls, P < 0.001), suggesting that efficacy against AF was because of prevention of tachy-cardiomyopathy-induced structural remodelling.

**Effects on cellular electrophysiology**

Direct cellular electrophysiological effects of angiotensin-II are controversial. L- and T-type Ca2+-current (I<sub>Ca,L</sub>, I<sub>Ca,T</sub>) regulation by angiotensin-II has been reported. Intracellular angiotensin-II reduced I<sub>Ca,L</sub> in rat ventricular cells, whereas the opposite was observed in hamsters. Intracellular angiotensin-II increases I<sub>Ca,L</sub> through PKC-dependent pathways. I<sub>Ca,T</sub> is increased by angiotensin-II stimulation. As I<sub>Ca,T</sub> blockade prevents AF-substrate development, renin-angiotensin system inhibition might be beneficial by preventing angiotensin-II-mediated I<sub>Ca,T</sub> increases. However, the lack of ACE-inhibitor benefit against 1-week atrial-tachycardia remodelling, in contrast to the clear benefit from the I<sub>Ca,T</sub>-inhibitor mibefradil in the same model, argues against an I<sub>Ca,T</sub>-inhibition mediated mechanism for ACE-inhibitor benefit for AF.

Modulation of K<sup>+</sup>-currents has also been reported. The rapid delayed-rectifier current (I<sub>Kr</sub>) in guinea pig ventricular myocytes is increased by clinically relevant concentrations of angiotensin-II (30 nmol/L), whereas the slow component (I<sub>Ks</sub>) is decreased. Transcriptional I<sub>Kr</sub>-downregulation is a hallmark of AF-induced electrical remodelling.

### Table 2: Direct ARB effects on ion currents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)/C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Conc. tested Effects at concentration tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4 mg/27.6 ng/L</td>
<td>No IC&lt;sub&gt;50&lt;/sub&gt; provided, single conc. tested</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>5 mg/107.5 ng/L</td>
<td>No IC&lt;sub&gt;50&lt;/sub&gt; provided, single conc. tested</td>
</tr>
<tr>
<td>Losartan</td>
<td>5 mg/49.7 ng/L</td>
<td>No IC&lt;sub&gt;50&lt;/sub&gt; provided, single conc. tested</td>
</tr>
<tr>
<td>E-3174, main active metabolite of Losartan; MW, molecular weight; C&lt;sub&gt;50&lt;/sub&gt;, half-maximal inhibitory concentration; Conc., concentration.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The AT\textsubscript{1} receptor forms a complex with Kv4.3 (the pore-forming ion-channel \(\alpha\)-subunit underlying the transient outward potassium current, \(I_{\text{to}}\)) and regulates its cell-surface expression.\textsuperscript{56} Stimulation of the receptor with angiotensin-II leads to internalization of the complex, which could contribute to \(I_{\text{to}}\)-reduction. Ventricular action potential duration (APD) is prolonged by angiotensin-II, and ACE-inhibitors reverse these changes while promoting cell-to-cell communication.\textsuperscript{57}

\textit{In vitro} studies with heterologously expressed K\textsuperscript{+}-channel subunits show varying effects of ARBs. Losartan blocks currents carried by HERG (corresponding to \(I_{\text{to}}\)), KvLQT1 and mINK (\(I_{\text{K}}\)) and hKv1.5 subunits (ultrarapid delayed-rectifier current, \(I_{\text{Kur}}\)).\textsuperscript{58} The drug prolongs guinea pig ventricular APD, whereas its metabolite E-3174 reduces APD.\textsuperscript{58} Candesartan, eprosartan, and irbesartan inhibit currents carried by hKv1.5, HERG, KvLQT1 + mink, and rKv4.3 subunits.\textsuperscript{59} While irbesartan blocks \(I_{\text{K}}\) and hKv1.5 at therapeutic concentrations, blockade of HERG and KvLQT1 + mink currents occurs only at supra-therapeutic levels (Table 2).\textsuperscript{50,61}

Overall, these observations suggest that the renin–angiotensin system could affect ion-channels, APD and impulse propagation, and facilitate re-entry. On the other hand, there is no measurable effect of acute angiotensin-II on propagation, and facilitate re-entry. On the other hand, stimulation of the receptor with angiotensin-II leads to internalization of the complex, which underlie the atrially expressed subunits.\textsuperscript{59} While irbesartan blocks \(I_{\text{K}}\) and hKv1.5 at therapeutic concentrations, blockade of HERG and KvLQT1 + mink currents occurs only at supra-therapeutic levels (Table 2).\textsuperscript{50,61}

Conclusions

Both ACE-inhibitors and ARBs appear to reduce AF incidence and may prevent AF-related complications. However, there are insufficient prospective double-blinded trial data and there is thus no solid clinical evidence to recommend ACE-inhibitor or ARB treatment solely for AF prevention at this time. Presently, ongoing clinical trials will help to understand the value of these drugs in AF management. Some issues remain to be studied on the basic science level. Clinical evidence demonstrates beneficial effects of ACE-inhibitor treatment in patients with risk factors for AF (e.g. heart failure, hypertension with LV hypertrophy). There is lack of experimental data addressing the effects of renin–angiotensin system inhibition applied after the development of such substrates. Furthermore, the effect of combining ARB and ACE-inhibitor treatment has not been studied.

The clinical anti-arrhythmic actions of ACE-inhibitors and ARBs may be mediated by prevention of structural remodelling. Direct ion-channel modulating properties might also contribute. Further studies of atrial remodelling changes and direct electrophysiological consequences of ACE-inhibitor and ARB therapy in human would be useful in elucidating clinically relevant mechanisms of action.

Conflict of interest: none declared.

References


Aortic dissection involving ostium of right coronary artery as the reason of myocardial infarction

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A 66-year-old woman was admitted after an episode of faint with concomitant severe chest pain lasting ~2 h. Typical retrosternal localization of the pain with ST-elevation (Pardee wave) in leads II, III, and aVF, and ST-depression in I, V1–V3 allowed to diagnose acute infero-posterior myocardial infarction. ECG also revealed temporal second-degree atrioventricular block (Mobitz II). Blood pressure was 140/70 mmHg and HR was 55 b.p.m. No distinct murmur was heard on cardiac auscultation. In coronary angiography, left coronary artery had no significant stenoses. After placing the catheter in the ostium of RCA, no severe stenosis was seen and the flow was normal (TIMI 3, MBG 3). Just after selective cannulation of the RCA, chest pain diminished and ST-elevation recovered. Of note, during the peak of dye injection, the lumen was distended and collapsed at the end of the injection in the proximal segment of the artery. However, in coronary angiography, the lumen of RCA seemed not to be narrowed significantly (Panel A). To thoroughly assess the vessel, intracoronary ultrasound (ICUS) was performed. No evident atheromatous plaque was present in proximal part of RCA. During manual pullback, a hypoechoic mass adjacent to proximal segment of the artery was clearly seen (Panel B). The lumen in proximal segment and in ostium of RCA was impressed and narrowed by that mass (Panel C). Such hypoechoic mass parallel to the artery is not normally seen at this site. It was suspected that false channel existed and was propagated from the aorta to the proximal part of RCA. Therefore, dissecting aneurysm of the aorta was strongly suspected. It is important that almost immediately after withdrawal of a catheter from the ostium of RCA, the signs of acute myocardial ischaemia (i.e. severe chest pain and ST-elevation) relapsed. We thought that the catheter kept the lumen of RCA patent enabling restoration flow through the artery. Computed tomography (CT) fully confirmed our diagnosis of dissecting aneurysm—revealing long dissection extending from aortic valve up to the renal arteries with false lumen being partly thrombosed. CT showed patent left coronary artery and lack of patency of the RCA (Panel D).

Comment: This case represents difficulties in diagnosis of aortic dissection. Acute myocardial infarction was diagnosed correctly but aetiology of myocardial ischaemia was not coronary artery disease as typical. In the presented case, information obtained from ICUS enabled to suspect aortic dissection involving ostium of RCA as the reason of acute myocardial infarction. The diagnosis was finally confirmed with CT.

Panel A. Coronary angiography: right coronary artery in RAO projection. Insignificant eccentric stenosis with smooth luminal border in the first segment of the artery.

Panel B. ICUS image: in the proximal segment of the RCA, intimal thickening and no atheromatous plaque is visible. Hypoechoic mass (white asterisk) adjacent to the RCA is present.

Panel C. ICUS image: hypoechoic mass (white asterisk) impressing and narrowing the ostium of RCA.

Panel D. CT image: true lumen (T) and false lumen (F) of aortic bulb, patent LCA (white arrow) and lack of patency of RCA (black arrow).