Myocardial infarction does not further impair renal damage in 5/6 nephrectomized rats


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Abstract

Background. Recent observational studies show that reduced renal function is an independent risk factor for the development of cardiovascular disease. Previously, we reported that myocardial infarction (MI) indeed enhanced mild renal function decline in rats after unilateral nephrectomy (NX) and that RAAS intervention inhibited this decline. The effects of an MI on pre-existing severe renal function loss and the effects of RAAS intervention interrupting this hypothesized cardiorenal interaction are however unknown and clinically even more relevant.

Methods. Male Wistar rats underwent MI, sham MI, 5/6NX, or 5/6NX and MI. Six weeks later, the NX rats were treated with an angiotensin-converting enzyme inhibitor (ACEi) or vehicle for 6 weeks.

Results. An MI did not significantly induce more proteinuria (303 ± 46 versus 265 ± 24 mg/24 h) and glomerulosclerosis (40 ± 11 versus 28 ± 4 arbitrary units) in 5/6NX+MI compared to 5/6NX, and ACEi therapy was equally effective in reducing renal damage in these groups. In the 5/6NX+MI group, decreased renal blood flow and creatinine clearance were observed compared to 5/6NX (2.2 ± 0.6 versus 3.6 ± 0.4 ml/min/kg and 2.1 ± 0.3 versus 2.9 ± 0.3 ml/min/kg), which both increased after ACEi to levels comparable found in the group that underwent 5/6NX alone.

Conclusions. MI does not further deteriorate structural renal damage induced by 5/6NX compared with 5/6NX alone. Furthermore, renal haemodynamic impairment occurs after MI, which can be improved applying ACEi therapy. Therefore, we conclude that treatment with ACEi should be optimized in patients with chronic kidney disease after MI to improve renal function.

Keywords: 5/6 nephrectomy; ACEi therapy; cardiorenal interaction; myocardial infarction

Introduction

An intriguing interaction is present between the heart and the kidney when either organ function is compromised. Clinical studies indicate that high serum creatinine levels, as an intrinsic measure for renal damage, and decreased filtration ability are independent risk factors for the development of cardiovascular disease [1,2]. Conversely, a myocardial infarction (MI) may lead to decreased renal function and therefore an increase in serum creatinine levels [3,4]. Both mechanisms are thought to induce a vicious circle of cardiorenal interaction, which may account for increased morbidity and mortality in patients with cardiovascular and renal disease. Several mechanisms have been hypothesized including haemodynamic alterations: involvement of the RAAS, the endothelin and the sympathetic nervous system, endothelial dysfunction, NO, reactive oxygen species and inflammation [5], which are also thought to interact with each other. First, as far as the role of haemodynamics in explaining the observed cardiorenal interaction is concerned, reduced cardiac output after MI may lead to reduced renal perfusion, which in turn could lead to compensatory RAAS activation. This RAAS activation in turn can be detrimental to both heart and kidneys. An elevated angiotensin II level is known to interact with cardiac function leading to progressive cardiac function loss [6], and elevated angiotensin II levels may lead to progressive renal damage [7]. RAAS intervention by angiotensin-converting enzyme inhibitors (ACEi) might be able to interrupt this vicious circle.

The effect of renal function loss on the heart has been investigated in experimental and clinical studies [1,8–13]. The effect of the opposite, effects of cardiac function loss on renal outcome, has been studied only in experimental settings so far. In our laboratory, we recently observed progressive proteinuria after MI in uninephrectomized rats [3], which gives only mild renal function impairment, and this proteinuria showed to be responsive to ACEi [14]. The importance of this model is that with further deterioration of renal function one would assume that cardiac risk even further increased, thus establishing a vicious circle. In this perspective, it is thus far not known if an MI compromises...
renal function even more in rats with already more severe renal damage. Therefore, the aim of the present study was to investigate whether an MI would further increase proteinuria and end-stage renal damage measured as focal glomerulosclerosis in rats with already a high serum creatinine level (and therefore low creatinine clearance) induced by 5/6 nephrectomy. In addition, we explored whether RAAS intervention could interfere in this interaction and therefore improve renal outcome after MI.

Subjects and methods

Experimental protocol

Male Wistar rats (275–350 g; n = 95) were housed under standard conditions with free access to food and drinking water. Rats received a standard chow diet. Animal experiments were approved by the institutional animal ethical committee.

Rats were divided into four groups: (1) 5/6NX+MI (n = 28), (2) 5/6NX (n = 29), (3) MI (n = 14) and (4) sham MI (n = 9). At T = 0 weeks 5/6NX, and at T = 2 weeks MI or sham MI were performed (Figure 1). After 6 weeks, rats with 5/6NX (groups 1 and 2) were randomized based on proteinuria into a vehicle group (VEH n = 13 or 14) and a group treated with lisinopril (Merck, Sharp & Dohme, Haarlem, The Netherlands) 2.5 mg/kg/day in the drinking water (ACEi n = 15). In all groups, the experiment was ended at T = 12 weeks.

At the end of the experiment, functional cardiac parameters were measured under 2.5% isoflurane anaesthesia, laparotomy was performed, renal blood flow was measured and afterwards the rats were exsanguinated by taking blood samples from the abdominal aorta for plasma measurements. The remaining kidney was flushed with saline and the heart and kidney were removed and weighed.

Surgical interventions

The 5/6 nephrectomy was performed by taking out one kidney and by ligation of two of the three branches of the contralateral kidney under anaesthesia with 2.0% isoflurane in N2/O2 (2:1) as described before [15–17]. Before the induction of MI, rats were intubated, ventilated (AIV, Hoek/Loos, The Netherlands) and anaesthetized using 2.0% isoflurane in O2. MI was induced by ligation of the left anterior descending coronary artery (LAD) as described previously [18–20].

Functional parameters

Urine, plasma and tissue measurements

For the measurement of urinary total protein excretion, 24-h urine samples were collected in metabolic cages at baseline, before start of therapy and at the end of the experiment. Urinary total protein was analysed using end-point measurement with TCA (Nephelometer Analyzer II, Dade Behring, Marburg, Germany). As a measure for renal function, creatinine clearance was investigated. For the calculation of creatinine clearance, urinary creatinine and plasma creatinine levels were measured at baseline, before start of therapy and at the end of the experiment. Creatinine was determined using photometric determination with the Jaffe method (Ecoline Mega, DiaSys Diagnostic Systems GmbH, Holzheim, Germany).

Haemodynamic, cardiac and renal characteristics

Systolic blood pressure (SBP) was measured using tail-cuff plethysmography (IITC Life Science, Woodland Hills, CA, USA) in trained awake, restrained animals. SBP was measured at baseline, before start of therapy and at the end of the experiment.

Cardiac performance was measured with a pressure transducer catheter under anaesthesia, (2.5% isoflurane in O2) inserted through the right carotid artery (Micro-Tip 3 French, Millar Instruments Inc., Houston, TX, USA), connected to a personal computer equipped with an analogue-to-digital converter and appropriate software (Millar Instruments, Germany). After a 3-min period of stabilization, left ventricular end diastolic pressure (LVEDP) and left
ventricular peak systolic pressure (LVSP) were recorded. Thereafter, the catheter was withdrawn into the aortic root to measure SBP. As a parameter of global myocardial contractility and relaxation, we determined the maximal rates of increase and decrease in left ventricular pressure (systolic +dP/dt max and diastolic −dP/dt max) that were normalized to left ventricular pressure change (i.e. LVSP-LVEDP) for individual rats.

Renal blood flow was measured at the end of the study to investigate the effects of ACEi therapy in the 5/6NX and 5/6NX+MI group on renal blood flow using a 1-mm flow probe around the left renal artery (1RB; Transonic, Ithaca, NY, USA), connected to a flow meter (T106 Small Animal Research Flow meter; Transonic, Ithaca, NY, USA).

**Histology**

**Kidney**

Kidneys were fixed by immersion for 48 h in a 4% buffered formaldehyde solution (Klimipath, Duiven, The Netherlands) after longitudinal bisection and subsequently embedded in paraffin according to standard procedures. Sections of 3 µm were stained with periodic acid Schiff (PAS). The degree of mesangial matrix expansion (MME) and focal glomerulosclerosis were assessed in 50 glomeruli by scoring semi-quantitatively on a scale of 0–4. MME was scored positive when mesangial matrix expansion was present. Focal glomerulosclerosis was scored positive when mesangial matrix expansion and adhesion to Bowman’s capsule were present in the same quadrant. When 25% of the glomerulus was affected, a score of 1+ was adjudged, 50% was scored as 2+, 75% as 3+ and 100% as 4+. The overall MME and focal glomerulosclerosis score is expressed as arbitrary units (AU) with a maximum of 200. Interstitial fibrosis (IF) was defined as expansion of the interstitial space, with or without the presence of atrophied and dilated tubules and thickened tubular basement membranes. The degree of IF was assessed at 20× magnification by scoring semi-quantitatively on a scale of 0–5; 0: no IF, 1: 1–10%, 2: 10–25%, 3: 25–50%, 4: 50–75% and 5: 75–100% IF. The score is given as the mean of the scored slices. An examiner blinded for the groups evaluated all sections.

Interstitial alpha-smooth muscle actin (α-SMA) was determined as a profibrotic marker and detected in paraffin-embedded sections by means of a mouse monoclonal α-SMA antibody (Sigma Chemical, St Louis, MO, USA). First, the antibody was incubated for 60 min and its binding was detected by sequential incubations with peroxidase (PO)-labelled rabbit anti-mouse and PO-labelled goat anti-rabbit antibody (both from Dakopatts, DAKO, Glostrup, Denmark) for 30 min. The expression of interstitial α-SMA was measured by computerized morphometry. Therefore, 40 fields were scored at ×20 magnification in the cortical region; glomeruli and vessels were excluded from measurement along Bowman’s capsule and the vessel wall. Total staining was expressed as the percentage of the total area.

**Heart**

The heart was arrested in diastole in a cold 1 M KCl solution and weighed. The ventricles were dissected from the atria, and the right free wall was separated from the left ventricle. A left ventricular mid-sagittal slice (of ~2 mm) was fixed in 4% buffered formaldehyde solution, embedded in paraffin, cut into 5 µm slices and stained with 0.1% Sirius Red F3B and 0.1% Fast Green FCF (Klimipath, Duiven, The Netherlands). Endo- and epicardial circumference of the left ventricle and scar tissue was determined by means of a computerized planimeter (Image-Pro plus, Media Cybernetics Inc., Bethesda, MD, USA). MI size was expressed as the sum of scar lengths divided by the total left ventricular circumference, and all sections were evaluated by an examiner blinded for the groups. Deparaffinized 5-µm-thick transverse cardiac sections at the midventricular level were stained with Lectin GSL staining (Sigma-Aldrich) to stain endothelial cells for analysis of capillary density. Capillary density was obtained by counting the number of capillaries per total tissue area (No/mm²).

**Calculations and statistical analysis**

All data are presented as mean ± SEM. If normally distributed, differences between the groups were compared using a one-way ANOVA, followed by a Fisher’s protected LSD post hoc test to identify the groups that were different from each other; otherwise a non-parametric test was used. The effect of ACEi was tested with an independent sample t-test compared to the vehicle-treated group, or if the data were not normally distributed with a non-parametric Mann–Whitney test. To identify differences in one animal between two time points, a paired sample t-test was used, when the data was not normally distributed, a Wilcoxon signed ranks test was used. In all tests, P < 0.05 was considered statistically significant.

**Results**

**Survival and overall condition**

All animals survived the nephrectomy. In the 5/6NX group, out of 39 animals that additionally received an MI, 28 survived and 11 animals died within 1 day after MI. In the group receiving only an MI, 4 out of 18 animals undergoing surgery died within 1 day. All sham-operated animals recovered well after surgery. At the end of the 12-week follow-up, the animals in the 5/6NX+MI group had a significantly lower body weight compared to the other groups (Table 1). Treatment with ACEi did not influence bodyweight in 5/6NX and 5/6NX+MI (Table 2).

**Cardiorenal interaction: effects on the kidney**

Renal effects were assessed by proteinuria, kidney weight, renal histology and creatinine clearance. Compared to sham-operated animals, MI did not induce a change in these renal parameters (Table 1 and Figures 2B and 3). The 5/6NX alone resulted in renal damage, as demonstrated...
by an increased proteinuria from 19 ± 3 mg/24 h at baseline to 265 ± 24 mg/24 h, and increased kidney weight, focal glomerulosclerosis, mesangial matrix expansion, IF and interstitial α-SMA (Figures 2B and 3), and a significantly decreased creatinine clearance from 5.5 ± 1.3 ml/min/kg at baseline to 2.9 ± 0.3 ml/min/kg (Table 1).

In the 5/6NX+MI group, additional changes in renal parameters were noted compared to 5/6NX. While kidney weight, proteinuria, focal glomerulosclerosis, mesangial matrix expansion, IF and interstitial α-SMA were comparable between these groups, a further decline in creatinine clearance (P = 0.05) and renal blood flow (2.2 ± 0.6 versus 3.6 ± 0.4 ml/min/kg) was observed in the 5/6NX+MI group compared to sole 5/6NX (Figure 4). Thus, cardiorenal interaction resulted in no increase in renal damage measured as proteinuria and glomerular and interstitial damage, while an additional change in renal haemodynamic function was observed as demonstrated by reduced clearance and reduced renal blood flow.

Cardiorenal interaction: effects on the heart

Compared to sham, the MI group displayed cardiac hypertrophy and a decrease in cardiac function. Left ventricular end diastolic pressure (LVEDP) was higher compared to sham-operated animals (P = 0.06), and cardiac contractility (+dP/dt max, P = 0.1) and cardiac dilation (−dP/dt max, P < 0.01) were lower. Heart weight was significantly higher after MI compared to sham (Figure 2A), while cardiac capillary density was lower after MI.

Following 5/6NX, both systolic and diastolic blood pressures were significantly higher compared to sham-operated animals (Table 1). Further, 5/6NX impaired cardiac contractility and cardiac dilation and increased heart weight (Figure 2A) to a level comparable to the cardiac hypertrophy after MI. Cardiac capillary density was increased after 5/6NX compared to sham and compared to MI.

In the 5/6NX+MI group, additional changes in cardiac parameters were observed compared to the 5/6NX group and the MI group. While cardiac function parameters did not differ, 5/6NX+MI featured a significant increase in by an increased proteinuria from 19 ± 3 mg/24 h at baseline to 265 ± 24 mg/24 h, and increased kidney weight, focal glomerulosclerosis, mesangial matrix expansion, IF and interstitial α-SMA (Figures 2B and 3), and a significantly decreased creatinine clearance from 5.5 ± 1.3 ml/min/kg at baseline to 2.9 ± 0.3 ml/min/kg (Table 1).

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A

Effect of cardiac and renal damage on heart weight and kidney weight. White bar: sham, black bar: MI, light grey bar: 5/6NX, dark grey bar: 5/6NX+MI, striped bars: ACEi treatment. The weight of a single kidney is given for all groups. *P < 0.05 versus sham and in panel B versus sham and MI, **P < 0.05 versus all other groups, #P < 0.05 versus vehicle-treated animals.

B

renal histology with representative pictures. Panel A: focal glomerulosclerosis and mesangial matrix expansion, panel B: interstitial α-smooth muscle actin staining, panel C: interstitial fibrosis. White bar: sham, black bar: MI, light grey bar: 5/6NX, dark grey bar: 5/6NX+MI, striped bars: ACEi treatment. *P < 0.05 versus sham and MI, #P < 0.05 versus vehicle-treated animals.

cardiac hypertrophy (Figure 2A) and a decrease in cardiac capillary density (Table 3) compared to sole 5/6NX or sole MI. Thus, cardiorenal interaction resulted in an excess cardiac hypertrophy.

Effect of RAAS intervention on the vicious circle after cardiac and renal function loss

To investigate whether intervention in the RAAS by ACE inhibition is effective in interrupting the hypothesized vicious circle of cardiac and renal impairment, the above mentioned parameters were studied in 5/6NX and 5/6NX+MI groups treated for 6 weeks with lisinopril or vehicle. Treatment with lisinopril effectively normalized the blood pressure in 5/6NX from 146 ± 6 mmHg to 115 ± 4 mmHg (P < 0.001), and in the 5/6NX+MI from 143 ± 6 to 122 ± 7 mmHg (P = 0.02). In both 5/6NX and 5/NX+MI, plasma renin activity was increased comparably after ACEi treatment (Table 3).

ACEi treatment prevented renal damage to a similar extent in 5/6NX and 5/6NX+MI, as demonstrated by a similar reduction in proteinuria (Table 2) and a significantly lower interstitial α-SMA (Figure 3B), while a trend
Fig. 4. Effect ACEi treatment on renal blood flow and creatinine clearance in 5/6NX and 5/6NX+MI. Light grey bar: 5/6NX, dark grey bar: 5/6NX+MI, striped bars: ACEi treatment. *P < 0.05 versus 5/6NX, #P < 0.05 versus vehicle treated animals.

Table 3. Haemodynamic characteristics after treatment with ACEi

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5/6NX</th>
<th>5/6NX+MI</th>
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<tbody>
<tr>
<td></td>
<td>VEH</td>
<td>ACEi</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>MI size (%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>146 ± 6</td>
<td>115 ± 4*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>104 ± 5</td>
<td>81 ± 4*</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>151 ± 6</td>
<td>125 ± 4*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>11.5 ± 0.9</td>
<td>12.5 ± 0.8</td>
</tr>
<tr>
<td>+dP/dt max (s⁻¹)</td>
<td>94 ± 3</td>
<td>106 ± 3*</td>
</tr>
<tr>
<td>−dP/dt max (s⁻¹)</td>
<td>−85 ± 2</td>
<td>−91 ± 2</td>
</tr>
<tr>
<td>Plasma renin activity (ngAI/ml/h)</td>
<td>6 ± 2</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>Cardiac capillary density (no × 10³/mm²)</td>
<td>3.9 ± 0.7</td>
<td>4.0 ± 0.6</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM. MI, myocardial infarction; 5/6NX, 5/6th nephrectomy; VEH, vehicle; ACEi, ACE inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVSP, left ventricular peak systolic pressure; LVEDP, left ventricular end diastolic pressure.

*P < 0.05 versus VEH.

bP < 0.05 versus 5/6NX.

towards lower focal glomerulosclerosis (5/6NX P = 0.07, 5/6NX + MI P = 0.1) and mesangial matrix expansion (5/6NX P = 0.07, 5/6NX + MI P = 0.1) was observed (Figure 3A). ACEi had no significant effect on IF (Figure 3C). Moreover, while ACEi treatment did not affect creatinine clearance and renal blood flow in the 5/6NX group, it normalized the decrease in both parameters observed in the 5/6NX+MI group (Table 3). Furthermore, while functional cardiac parameters were unaffected by the therapy (Table 3), ACEi treatment significantly reduced cardiac hypertrophy in 5/6NX and 5/6NX+MI groups (Figure 2A). ACEi therapy did increase cardiac capillary density in the 5/6NX+MI group, while no influence was observed in the 5/6NX group (Table 3).

Discussion

This is the first experiment in which the long-term renal effect of cardiac function loss was established in animals with already severely impaired kidney function to explore a vicious circle between the heart and the kidney. Moreover, it is the first time that the protective effects of ACEi in combined severe cardiac and renal damage were established.
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and interstitial focal glomerulosclerosis, mesangial matrix expansion, IF tomized rats with additive MI: proteinuria, kidney weight, no increase in renal damage was observed in the nephrectomized rats with an additive MI, which is thought to be associated with angiotensin II levels [34]. An elevated angiotensin II level is known to interact with cardiac function leading to progressive cardiac function loss [6]. In addition, elevated angiotensin II may lead to progressive renal damage [7] and a decrease in capillary length density [32,33] in experimental renal failure. In this study an increase in cardiac capillary density was found, which is not in line with this literature.

Cardiac function loss caused by MI did lead to a further decrease in creatinine clearance and renal blood flow. Apparently, reduced cardiac output after MI may lead to reduced renal perfusion, which in turn could lead to compensatory RAAS activation. This is confirmed by the decrease in renal blood flow observed in the nephrectomized rats with an additive MI, which is thought to be associated with angiotensin II levels [34]. An elevated angiotensin II level is known to interact with cardiac function leading to progressive cardiac function loss [6]. In addition, elevated angiotensin II may lead to progressive renal damage [7] as well, resulting in a vicious circle. In the current study, no increase in renal damage was observed in the nephrectomized rats with additive MI: proteinuria, kidney weight, focal glomerulosclerosis, mesangial matrix expansion, IF and interstitial α-SMA staining were comparable in both 5/6NX and 5/6NX+MI. Blood pressure was comparable in both groups as well. This phenomenon could be explained by the RAAS activation after renal ablation by 5/6 nephrectomy: in an animal with an already highly activated RAAS, an MI will not lead to more RAAS activation and therefore not to more renal damage. A plateau of damage is reached. This is confirmed by the comparable amount of renin activity in both 5/6 nephrectomized rats and 5/6 nephrectomized rats plus MI. Out of the previous could be concluded that no vicious circle is activated after MI in animals with already-established renal function loss.

We found a higher mortality from MI in the 5/6 nephrectomized rats than in the sham group. This might be explained by a decreased ischaemia tolerance in 5/6 nephrectomized rats. Dikow et al. found that a greater proportion of nonperfused myocardium underwent total necrosis after MI in 5/6 nephrectomized rats [6], which could lead to a higher mortality after MI in these rats.

RAAS intervention with either the ACEi or angiotensin receptor blocker is known to protect both heart and kidney [35,36]. However, in the clinical situation, ACE inhibitors are not always prescribed to patients with combined renal and heart failure, while ACE inhibitors improve the long-term outcome on cardiovascular morbidity and mortality [37,38]. Therefore, it is of the utmost importance to get insight into the pharmacological effects of ACEi in combined cardiac and renal damage. In a model with both severe renal and cardiac function loss, a dual or combined activation of the RAAS is present. Thus far, the effects of RAAS intervention with ACEi on cardiac and renal outcome in the model mentioned are unknown. In the current study, ACEi therapy was very effective in both 5/6NX and 5/6NX+MI in reducing haemodynamic parameters, like SBP, DBP, LVSP and cardiac hypertrophy. Moreover, it was effective in reducing renal damage, i.e. proteinuria, focal glomerulosclerosis and interstitial α-SMA staining. Besides these comparable effects, ACEi therapy was able to restore the impaired creatinine clearance and renal blood flow in 5/6NX+MI to the levels in sole 5/6NX. These results are in favour of the important role of RAAS stimulation after 5/6 nephrectomy and MI to decrease renal function and renal blood flow. Besides the beneficial effects on renal function, ACEi therapy was able as well to increase cardiac capillary density in animals with 5/6NX+MI. It should, however, be taken into account that RAAS inhibition is invariably associated with blood pressure reduction. Therefore, lowering blood pressure by means of a calcium channel blocker would be an interesting strategy to further allow for a distinction between blood pressure lowering per se and blockade of the RAAS.

In conclusion, our results showed that an MI did not cause a decrease in structural renal function in animals with already severely decreased renal function. The responsiveness of renal damage to RAAS intervention was comparable between combined cardiac and renal function loss and sole renal function loss. Although no difference in renal function could be observed, a detrimental haemodynamic effect of an additive MI to nephrectomized rats on creatinine clearance and renal blood flow was observed, which showed to be responsive to ACEi therapy. Therefore, our study supports the view that a great concern is needed in the treatment of patients with renal disease to prevent further decline in renal function, because these patients are already more prone to experience an MI. In addition, ACE inhibitor therapy should be prescribed after MI in patients with compromised renal function to prevent a further decline in renal haemodynamics caused by combined cardiac and renal damage. The hesitation to treat a cardiac patient with high serum creatinine levels with RAAS intervention should thus be re-evaluated [38], since it is in fact those subjects that are at the highest risk and need these therapies the most.
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