LIFE
The Losartan Intervention For Endpoint Reduction in Hypertension Study

On behalf of the Steering committee and all Investigators UPDATE on LIFE
Björn Dahlöf
Göteborg
Conflict of Interest statement

I do not consider that I have a conflict of interest in connection with this paper insofar as I do not believe that any relationships, competition, or commitments that I have, have biased my input into or objective judgement of this work. However I declare that I have served as a consultant and have had speaking engagements, not necessarily related to this topic, to most pharmaceutical companies, including the sponsor of this study, marketing CV drugs and have been compensated for travel, time spent on research and lectures. Nor me neither any of my family have any propriety interest or own any stock in any pharmaceutical or device company.
LIFE
The Losartan Intervention For Endpoint Reduction in Hypertension Study

On behalf of the Steering committee and all Investigators

UPDATE on LIFE
Björn Dablöf
Göteborg
LIFE: Study Drug and Characteristics
Losartan-based vs Atenolol-based therapy

Mean Dosage:
- Losartan 82 mg
- Atenolol 79 mg

Combination therapy in a majority
All other medication similar between treatment arms

N= 9193
Hypertension
ECG-LVH
174/98 mmHg
54% women
13% diabetics
14% ISH
16% CHD
8% CVD incl TIA

Investigator-initiated
Prospective
R, DB, PG
945 centers
4.8 years

Time on drug
84 %
80 %

B Dahlöf et al Lancet 2002;359:995-1003
Recent Hypertension Trials With “New” Versus “Old” Drugs

Primary Endpoint (RR ± 95% CI)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>RR</th>
<th>CI</th>
<th>P</th>
<th>N</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPPP</td>
<td>captopril</td>
<td>0.52</td>
<td>(0.40-0.68)</td>
<td>0.52</td>
<td>10,985</td>
<td>Lancet 1999</td>
</tr>
<tr>
<td>STOP-2</td>
<td>ACEIs/CCBs</td>
<td>0.89</td>
<td>(0.77-1.03)</td>
<td>0.89</td>
<td>6,614</td>
<td>Lancet 1999</td>
</tr>
<tr>
<td>NORDIL</td>
<td>diltiazem</td>
<td>0.97</td>
<td>(0.85-1.12)</td>
<td>0.97</td>
<td>10,948</td>
<td>Lancet 2000</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>nifedipine GITS</td>
<td>0.34</td>
<td>(0.25-0.45)</td>
<td>0.34</td>
<td>6,321</td>
<td>Lancet 2000</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>doxazosin</td>
<td>0.71</td>
<td>(0.61-0.82)</td>
<td>0.71</td>
<td>24,335</td>
<td>JAMA 2000</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>verapamil COER</td>
<td>0.77</td>
<td>(0.65-0.92)</td>
<td>0.77</td>
<td>16,602</td>
<td>JAMA 2003*</td>
</tr>
<tr>
<td>LIFE</td>
<td>losartan</td>
<td>0.021</td>
<td>(0.013-0.034)</td>
<td>0.021</td>
<td>9,193</td>
<td>Lancet 2002</td>
</tr>
</tbody>
</table>

Favors Diuretics / βBlockers Favors “New” Drugs

*Black HR et al. JAMA. 2003;289:2073-2082.
LIFE Benefit vs no treatment

- Estimated yearly CV absolute risk at baseline about 4%
- Observed yearly CV absolute risk on study treatment about 2%
  - 50% average relative risk reduction for a clinical BP reduction of 30/17 mm Hg
- Additional significant further relative risk reduction from choice of the losartan therapeutic strategy
  - Primary composite 13%
  - Stroke 25%
  - New onset DM 25%

For the same BP lowering and better tolerability
How to design a study to show that it matters how you lower blood pressure?

- Randomised comparison of two antihypertensive treatment strategies in high risk
- Comparison being established cost-effective
- Clinically relevant endpoints
- ”Equal” blood pressure control; clinic BP 24 ABP
- Similar use of other antihypertensive agents
- Similar use of other drugs (e.g. Statins, Aspirin)
- A plausible mechanism
LIFE Substudy: 24-Hour Ambulatory Blood Pressure - Systolic Pressure

Mean 24-Hour Systolic Blood Pressure at Year 1

<table>
<thead>
<tr>
<th></th>
<th>Losartan (n=57)</th>
<th>Atenolol (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>136.1</td>
<td>134.7</td>
</tr>
</tbody>
</table>

FDA Jan 6, 03
Stroke in LIFE
LIFE: Fatal/Nonfatal Stroke

Losartan
Atenolol

Risk Reduction 24.9%, p=0.001

Study Day

Endpoint Rate

0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08

Intention-to-Treat

Atenolol
N=309 (7%)

Losartan
N=232 (5%)

Risk Reduction 24.9%, p=0.001

B Dahlöf et al Lancet 2002;359:995-1003
LIFE: Investigator Classification of Strokes

Number of strokes (fatal and non-fatal)

\[ p = 0.002 \]

- Athero-Thrombotic
- Embolic
- Hemorrhagic

"Ischemic Stroke"
LIFE Stroke Prevention

Further reduction with Losartan based therapy

- With LVH: 25%
- Diabetes: 22%
- Without Vascular Disease: 34%
- ISH: 40%
- Atrial Fibrillation: 45%

For the same BP control
Stroke: A Preventable Catastrophe
The Need for European Action

European Parliament, Brussels, Belgium
19 June 2003
Population Impact of Losartan based Therapy in the EU

• Based on the LIFE study vs Atenolol

• Conservative estimate 78 million patients fulfil the LIFE criteria

• 125,000 strokes avoided in 5 years

• If 40% LVH 230,000 strokes avoided
LIFE: Atrial fibrillation
– Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Losartan (n=157)</th>
<th>Atenolol (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.0 (6.5)</td>
<td>70.9 (6.1)</td>
</tr>
<tr>
<td>Women</td>
<td>62 (41%)</td>
<td>75 (43%)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>176/97 (13/10)</td>
<td>176/98 (14/10)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (4.6)</td>
<td>27.6 (4.6)</td>
</tr>
<tr>
<td>Cornell voltage-duration product (mm x sec)</td>
<td>2915 (1296)</td>
<td>3142 (1414)</td>
</tr>
<tr>
<td>Framingham risk score</td>
<td>5.27 (2.2)</td>
<td>5.27 (2.1)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>20 (13%)</td>
<td>29 (16%)</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>41 (27%)</td>
<td>41 (24%)</td>
</tr>
<tr>
<td>Cerebral vascular disease, n (%)</td>
<td>19 (13%)</td>
<td>28 (16%)</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
<td>26% (33%)</td>
<td>214 (30%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>32 (21%)</td>
<td>48 (26%)</td>
</tr>
<tr>
<td>Isolated systolic hypertension, n (%)</td>
<td>27 (18%)</td>
<td>39 (23%)</td>
</tr>
</tbody>
</table>

* defined as systolic blood pressure ≥160 and diastolic blood pressure <90 mmHg
LIFE: Atrial fibrillation
Primary Composite Endpoint

Adjusted risk reduction: 43%, p=0.008
Unadjusted risk reduction: 42%, p=0.009

Intention-to-treat analysis

Wachtell K et al, Submitted 2003
Effect of Losartan versus Atenolol on LA Diameter: The LIFE Study

![Bar chart showing the comparison of LA diameter between Baseline and During Treatment for Losartan and Atenolol with a P-value of <0.001.]

Gerdts E et al Submitted 2003
**LIFE: New Onset Atrial Fibrillation**
- by Treatment Group

![Graph showing proportion of patients with first event (%) over time (months)].

- **Losartan**
- **Atenolol**

**RR**: 0.70 [95% CI: 0.58-0.85], p<0.001.

**Adj. RR**: 0.72 [95% CI: 0.59-0.89], p<0.001.

Wachtell K et al. Submitted 2004
Diabetes in LIFE
LIFE: Diabetes – Total Mortality

Intention-to-Treat
Risk Reduction = 39%; p=0·002

Atenolol
n=104 (17%)

Losartan
n=63 (11%)

Proportion of patients, %
Study Month

LIFE Diabetes and Sudden Death

Adjusted Risk Reduction = 51%, p=0.027
Unadjusted Risk Reduction = 54%, p=0.017

Atenolol
Losartan

Lindholm et al Lancet 2003; Aug 23
ARBs > ACEIs in Diabetes Type II
Results from UKPDS to LIFE

**UKPDS**
Captopril vs Atenolol based therapy
No difference

**STOP2**
ACEI vs beta-blocker/diuretic based therapy
No difference

**LIFE**
Losartan vs Atenolol based therapy
- 25% primary endpoint (ARR 5%)
- 39% mortality (ARR 6%)
- 51% sudden death
Kidney in LIFE
Ann Intern Med 2003;139:901-6
Albuminuria and CV risk in hypertensive patients with LVH: the LIFE study

• Conclusion: "Increased UACR resulted in increasing risk for cardiovascular morbidity and mortality............We found no thresholds or plateaus”

• Main findings: In non-diabetic patients, for every 10-fold increase in UACR

<table>
<thead>
<tr>
<th>Event</th>
<th>HR increase(95CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint</td>
<td>57% (40.6, 75.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>51% (28.8, 76.9)</td>
</tr>
<tr>
<td>MI</td>
<td>45% (19.9, 75.4)</td>
</tr>
</tbody>
</table>
LIFE Albuminuria: Endpoint Rate According to Deciles of Baseline Urine Albumin/Creatinine

Composite endpoint rate
Adj. composite endpoint rate*

* Adjusted for ECG LV mass, Framingham Risk Score and study treatment allocation
LIFE - Diabetics

Development of albuminuria

<table>
<thead>
<tr>
<th>Losartan</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>43 (7%)</td>
<td>79 (13%)</td>
</tr>
</tbody>
</table>

p< 0.002

Data on file BD 2003
Varia
in
LIFE
## LIFE: Primary Endpoint

### Baseline Subgroups - Test for Interaction with Treatment

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>p-Value</th>
<th>Subgroup</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.185</td>
<td>Smoking status</td>
<td>0.282</td>
</tr>
<tr>
<td>Gender</td>
<td>0.420</td>
<td>Alcohol intake</td>
<td>0.420</td>
</tr>
<tr>
<td>Country</td>
<td>0.607</td>
<td>Exercise status</td>
<td>0.892</td>
</tr>
<tr>
<td>Ethnic group</td>
<td>0.057</td>
<td>BMI</td>
<td>0.290</td>
</tr>
<tr>
<td><strong>Disease history</strong></td>
<td></td>
<td>Systolic BP</td>
<td>0.725</td>
</tr>
<tr>
<td>MI</td>
<td>0.316</td>
<td>Diastolic BP</td>
<td>0.402</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>0.211</td>
<td>Total cholesterol</td>
<td>0.975</td>
</tr>
<tr>
<td>IHD</td>
<td>0.209</td>
<td>HDL cholesterol</td>
<td>0.114</td>
</tr>
<tr>
<td>Angina</td>
<td>0.250</td>
<td>ECG-LVH (Cornell)</td>
<td>0.485</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.733</td>
<td>ECG-LVH (SL)</td>
<td>0.422</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.170</td>
<td>Framingham Risk</td>
<td>0.922</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.383</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>0.176</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-Vascular Disease

Primary Composite Endpoint

Adjusted risk reduction=19%, p=0.008
Unadjusted risk reduction=20%, p=0.006

CV mortality –20%
Stroke – 34%
New Onset DM – 31%

N = 6886
No clinically evident vascular disease
66 years
56% women
174/98 mmHg
Diabetes 11%
ISH 13%

Devereux RB et al Ann Intern Med 2003;139:169-177
Heart
in
LIFE
LIFE: ECG-LVH Regression from Baseline

Cornell Product

Losartan: p<0.0001
Atenolol

Sokolow-Lyon

Losartan: p<0.0001
Atenolol

B Dahlöf et al Lancet 2002;359:995-1003
ECG-LVH a surrogate endpoint

- Regression of Cornell Voltage Duration Product and/or Sokolow-Lyon criteria predicts lower CV event rates (LIFE 2002)

- Significantly greater regression of both LIFE criteria with losartan vs atenolol based therapy in the presence of comparable BP lowering (Okin P et al. Circulation 2003;108:684)
Regression of ECG-LVH in LIFE

Cornell Voltage Duration Product (mm×ms)

<table>
<thead>
<tr>
<th></th>
<th>Losartan (n=4591)</th>
<th>Atenolol (n=4561)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2826</td>
<td>2805</td>
</tr>
<tr>
<td>Change 1 year</td>
<td>-254</td>
<td>-111</td>
</tr>
<tr>
<td>Change 3 years</td>
<td>-313</td>
<td>-172</td>
</tr>
<tr>
<td>Change 5 years</td>
<td>-329</td>
<td>-180</td>
</tr>
</tbody>
</table>

Target Organ Damage According to ESH-ESC Guidelines on Hypertension

Left Ventricular Hypertrophy

**ECG**
Sokolow-Lyon > 38 mm
Cornell Voltage Duration Product > 2440 mm×ms
= LIFE criteria

**Echo**
LVMI > 125 g/m² for men
> 110 g/m² for women

J Hypertens 2003;21:1011-1053
LIFE Echo Substudy: Change in LV Mass

* p=0.007, adjusted for baseline LV Mass

<table>
<thead>
<tr>
<th>Change to Year in LIFE</th>
<th>Losartan</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change (g)

-50  -45  -40  -35  -30  -25  -20  -15  -10  -5  0  5  10  15  20  25  30  35  40  45  50
Mortality Stratified by Time-Varying Presence of Echo-LVH

LVH Absent
LVH Present

HR = 0.36
p < 0.001
95% CI 0.23 – 0.59

Mortality Stratified by Time-Varying Presence of Echo-LVH

LVH Absent
LVH Present

HR = 0.48
p = 0.031
95% CI 0.24 – 0.93

CV Death Stratified by Time-Varying Presence of Echo-LVH

LVH Absent
LVH Present

HR = 0.34
p = 0.004
95% CI 0.17 – 0.71

Cut-offs LVMI

116g/m² men
104g/m² women

Composite Endpoint Stratified by Time-Varying Presence of Echo-LVH

LVH Absent
LVH Present

HR = 0.58,
p = 0.008
95% CI 0.38 – 0.86

HR = 0.36
p < 0.001
95% CI 0.23 – 0.59

HR = 0.48
p = 0.031
95% CI 0.24 – 0.93

HR = 0.58,
p = 0.008
95% CI 0.38 – 0.86

HR = 0.34
p = 0.004
95% CI 0.17 – 0.71

Cut-offs LVMI

116g/m² men
104g/m² women

37
Mechanisms in LIFE
Explaining the LIFE results

Losartan beneficial effects > Atenolol

- Endothelial dysfunction +
- Vascular hypertrophy +
- Arterial stiffness +
- IMT +
- Fibrosis +
- LVH +
- Atrial Fibrillation +
- Central systolic BP +
- Anti-platelet action +
- Diabetes +
- Uric Acid +
Hemodynamic Factors
(Central and peripheral blood pressure)

Circulating Factors
(Glucose, Insulin, RBCs, PAI, TXA2, Uric Acid)

Cardiac remodeling/enlargement
(LV and L atria)

Vascular remodeling
(Hypertrophy, vascular lesions)

Endothelial Dysfunction

Hypocoagulatory State

Atrial Fibrillation
(emboli formation)

Atherosclerotic Plaques

Embolic Occlusion

Thrombotic Occlusion

Thrombus Formation

Ischemic Stroke

Plaque fragments
Plaque rupture

Losartan

Understanding Ischemic Stroke

Vascular Hemorrhage

Hemorrhagic Stroke
Balance

AT\textsubscript{1}-block

\begin{itemize}
\item Independent stroke prevention?
\item Facilitated nerve regeneration.
\end{itemize}
LIFE: New Onset Diabetes

Intention-to-Treat

Atenolol (N=3979)
Losartan (N=4019)

Risk Reduction 25%, p<0.001

B Dahlöf et al. Lancet 2002;359:995-1003
Losartan Unique?

Class-effect not proven
• SCOPE study weaker result than LIFE
• Uricosuric effect
• Anti-platelet effect
• Anti-inflammatory effect
LIFE study

The estimated net cost per QUALYs gained was Euro 7432

Jönsson B et al Abstract submitted
Antihypertensive therapy

Do not compare them - combine them!

First line Monotherapy discussion redundant
2003 ESH/ESC Guidelines

Consider:
Untreated BP level
Absence or presence of TOD and
risk factors
Choose between

Single agent
at low dose

Two-drug combination
at low dose

If goal BP not achieved

Previous
agent
at full dose

Switch to
different
agent at low dose

Previous
combination
at full dose

Add a third drug
at low dose

Two-three drug
combination

Full dose
monotherapy

If goal BP not achieved

Two-three drug
combination
at effective doses
JNC 7 on Combination Therapy

“The initiation of drug therapy with more than one agent may increase the likelihood of achieving the BP goal in a more timely fashion…”

(caution advised in those at risk for orthostatic hypotension)
Possible combinations of different classes of antihypertensive agents

2.8 drugs per patient

A majority of patients need combination therapy
LIFE in relation to current Guidelines on Hypertension provide information on:

- Choice of combination therapy
- Importance of effective BP reduction and control for prevention of CV Mortality and Morbidity
- Importance of TOD (LVH, microalbuminuria) for prognosis and evaluation of treatment
- A superior strategy for Stroke prevention
- A superior strategy for Diabetes prevention
- A superior strategy for AF prevention
- A superior strategy for protection in established NIDDM
Conclusion

Against a backdrop of all the latest large clinical trials

For optimal BP control and long-term protection the best documented available alternative, keeping in mind that combination therapy is needed in a majority,

Provided no other special indication like beta-blocker for CHD
Conclusion

Against a backdrop of all the latest large clinical trials

For optimal BP control and long-term protection the best documented available alternative, keeping in mind that combination therapy is needed in a majority,

would be Losartan + HCTZ

Provided no other special indication like beta-blocker for CHD
LIFE A rich source of data

- 64 full manuscripts published or in press
- >150 abstracts presented at major meetings
- ESH 2003: 4 posters and 4 oral presentations
- ESC 2003: 4 posters and 1 oral presentation
- AHA 2003: 1 poster and 6 oral presentations
- ISH 2004: 1 poster and 2 oral presentations
- **ACC 2004: 5 posters and 7 oral presentations**
- >50 planned future publications from Main study, Echo-substudy, Genetic substudy and ICARUS
- Additionally: Cost Effectiveness and Public Health data