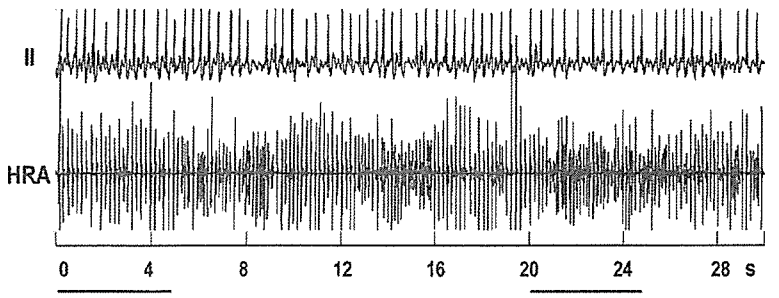


Fig 1. A 30-s set of atrial electrograms from the high right atrium (HRA) during atrial fibrillation filtered with a band pass of 30–400 Hz and the surface ECG lead II. The solid bold line at top left indicates the first 5 s of data at the beginning of the recording and at top right, a segment of the recording from 20 s to 25 s from the beginning of the recording. The atrial electrograms on the left are more organized than those on the right.

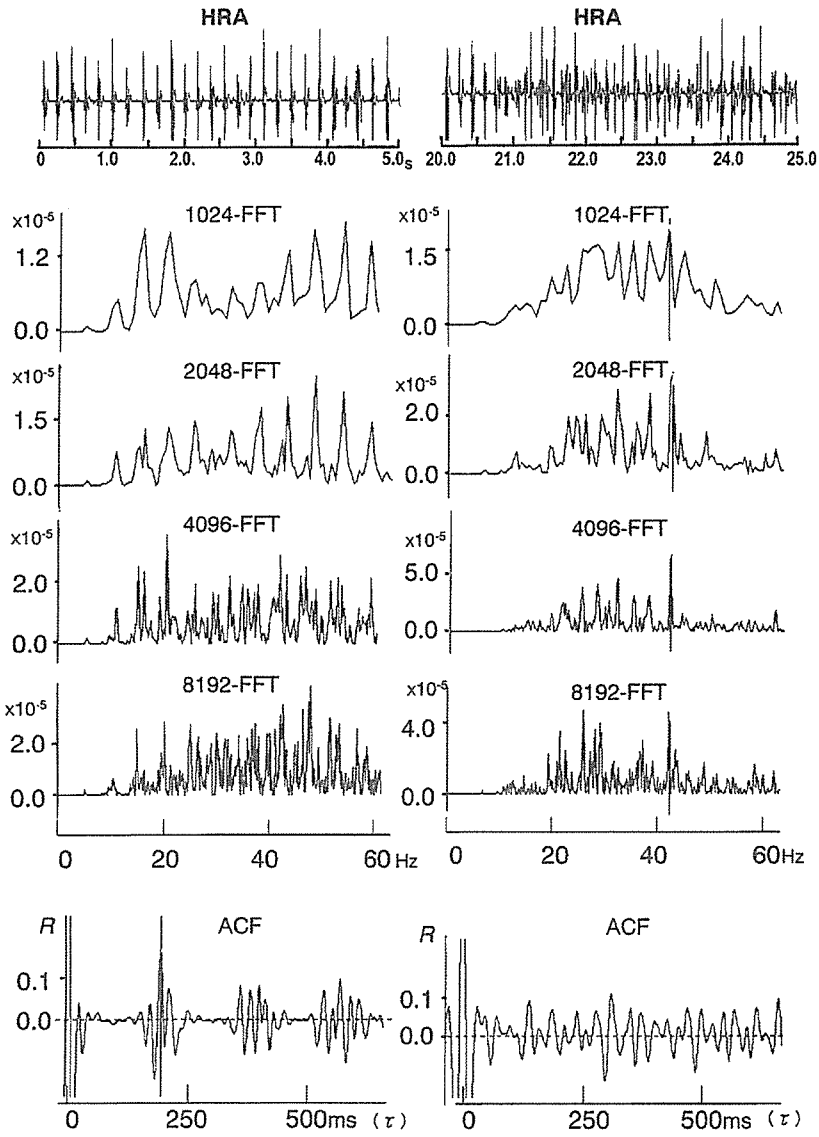


Fig 2. The 5-s raw atrial electrograms from the HRA with their corresponding FFT analyses performed with a Hamming window and ACF. (Upper panel) Raw atrial electrograms from the same 5-s strip of data shown in the top left and right bars in Fig 1. (Middle panel) 1,024-, 2,048-, 4,096- and 8,192-point FFT analyses based on each 5-s strip of atrial electrograms shown in the upper panel. (Bottom panel) ACF from each 5-s strip of atrial electrograms shown in the upper panel. HRA, high right atrium; FFT, fast Fourier transformation; ACF, autocorrelation function.

data. We also obtained the DFs of the 30-s data using a 4,096-point FFT (30 s-II) from the same rectified then low-pass filtered atrial electrograms to study the influence of signal averaging.

Linear regression analysis was used to examine the relationship between the DF and peak AFCL. In this study, the peak AFCL (ms) was expressed in Hz. The Kruskal-Wallis test was used to compare the DF in the different spectral analyses. The Wilcoxon signed-rank test was used to compare the influence of the low-pass filtered signals on the peak AFCL and coefficient R from the ACF. All results are presented as the mean ± SD. Statistical significance was established for $p<0.05$.

## Results

*FFT and ACF Analyses*

Fig 1 shows 30-s atrial electrograms from the HRA during AF, filtered with a band pass of 30–400 Hz, and the surface ECG lead II. A 5-s data set was selected arbitrarily

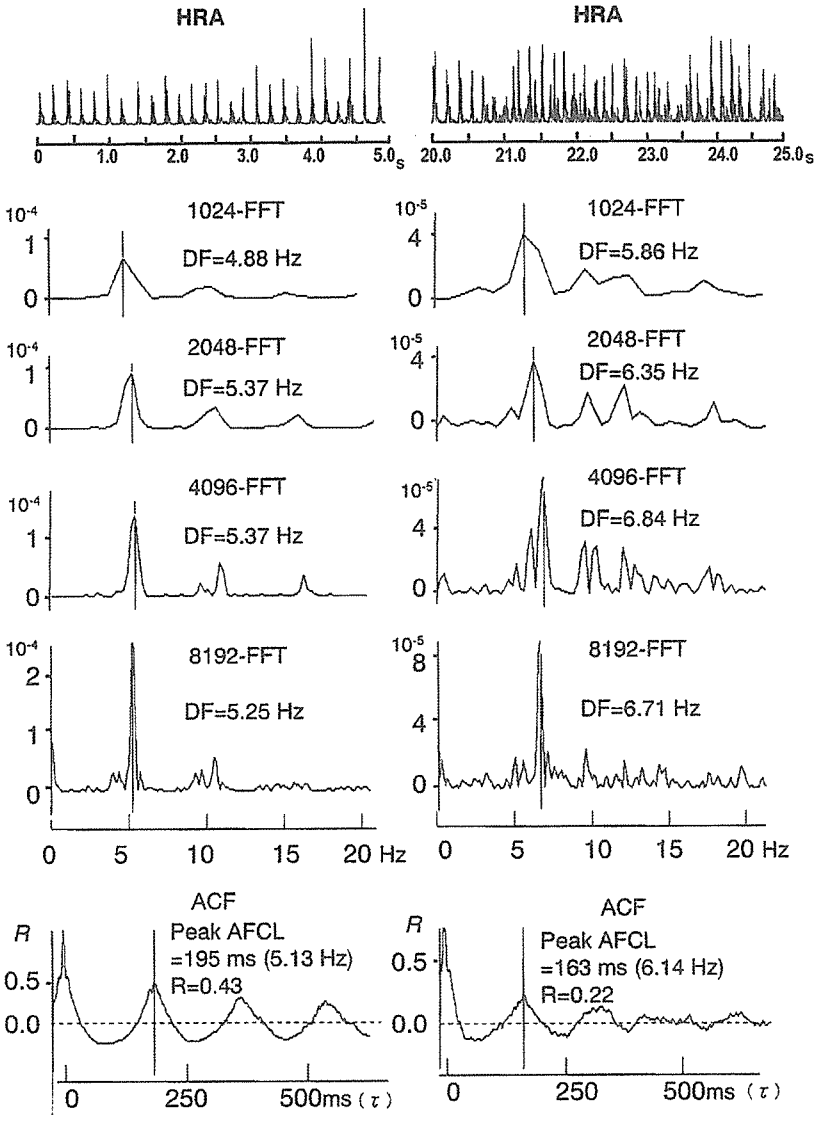


Fig 3. The 5-s rectified atrial electrograms from the HRA with their corresponding FFT analyses performed with a Hamming window and the ACF. See the text for details. HRA, high right atrium; FFT, fast Fourier transformation; ACF, autocorrelation function. DF, dominant frequency; peak AFCL, peak atrial fibrillation cycle length obtained from the ACF.

and is shown as a representative episode to compare the relatively organized and disorganized atrial electrograms.

Figs 2–4 shows 5 s each of the atrial electrograms, the 1,024, 2,048, 4,096 and 8,192-point FFT analyses and the ACF. In each Fig, the left panel shows the 4 types of FFT analyses and the ACF obtained from the same 5-s set of data (relatively organized) as shown in Fig 1 (Left). The right panel shows those obtained from the same 5-s data set (relatively disorganized) as shown in Fig 1 (Right).

Fig 2 shows the FFT analyses with a Mamming window and the ACF, using each 5 s of raw atrial electrograms. Multi-deflection signals were observed in each FFT analysis obtained from the organized and disorganized raw atrial electrograms. This resulted in difficulty in selecting the DF of each FFT analysis. The peak AFCL could hardly be identified in the left ACF (the vertical line in the bottom panel of Fig 2), and it could not be identified in the right ACF.

Fig 3 shows the FFT analyses with a Hamming window and the ACF, using the 5-s rectified atrial electrograms. In the FFT analysis, the number of peaks increased as the spectral resolution became higher. In each FFT analysis, the number of peaks increased more in the disorganized atrial electrograms than in the organized atrial electrograms. However, the DF in each FFT analysis was easily identified in both the organized and disorganized atrial electrograms. In each FFT analysis, the DF in the disorganized atrial electrograms was higher than that in the organized atrial electrograms; for example, the DF of the 4,096-point FFT analysis in the disorganized atrial electrograms (6.84 Hz) was higher than that in the organized atrial electrograms (5.37 Hz). The power spectral density in each FFT analysis obtained from the disorganized atrial electrograms was lower than that obtained from the organized atrial electrograms (Fig 3). In the ACF (Bottom panel), the peak AFCL (163 ms) and coefficient R at the peak AFCL (R=0.22) obtained from the disorganized atrial electrograms (Right panel) were less than the peak AFCL (195 ms) and coefficient R at the peak AFCL (R=0.43) obtained from the organized atrial electrograms (Left panel).

Fig 4 (Upper panel) shows the FFT analyses with a Hamming window and the ACF, using each of the 5-s rectified and then low-pass filtered (20 Hz) atrial electrograms. Each FFT analysis was exactly the same as that obtained from the 5-s rectified atrial electrograms (Fig 3). In the ACF analysis (Bottom panel), each peak AFCL

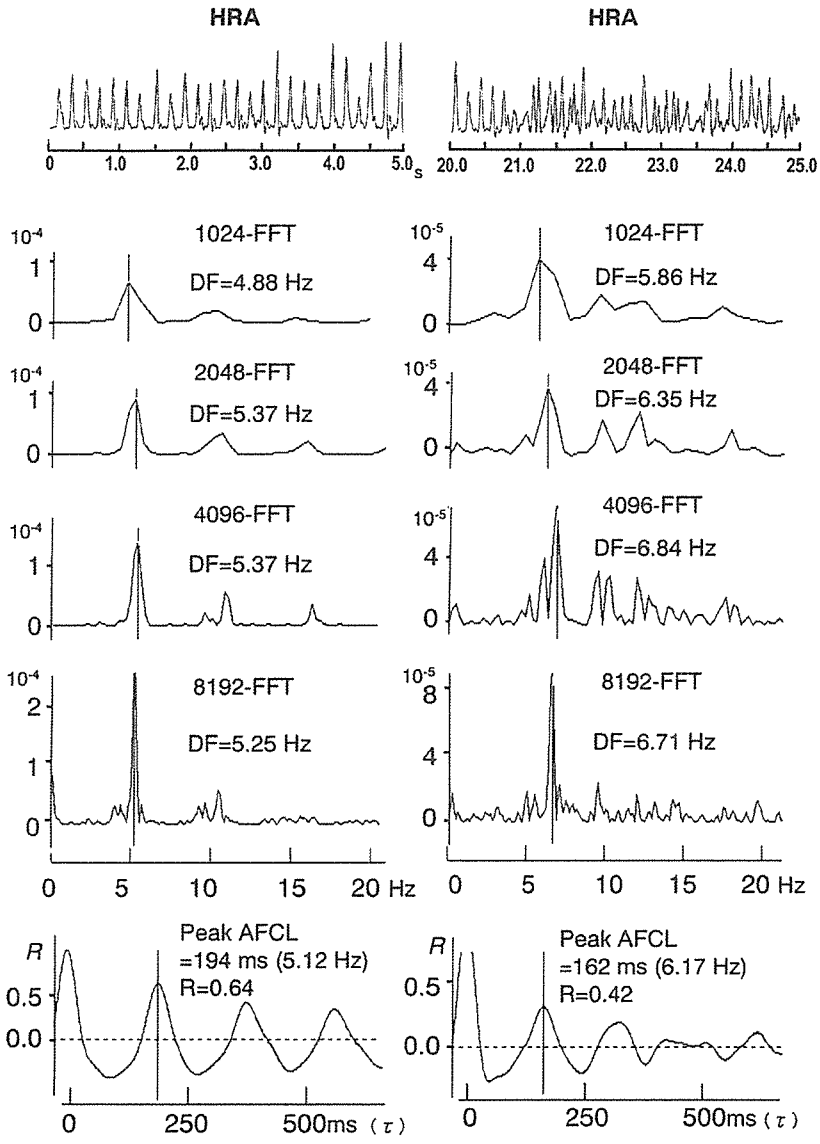


Fig 4. The 5-s rectified; and then low-pass filtered (20 Hz), atrial electrograms from the HRA with their corresponding FFT analyses performed with a Hamming window and the ACF. See the text for details. HRA, high right atrium; FFT, fast Fourier transformation; ACF, autocorrelation function; DF, dominant frequency; peak AFCL, peak atrial fibrillation cycle length obtained from the ACF.

obtained from the signals filtered with a low-pass was almost the same as that obtained from the signals filtered without a low-pass (194 ms vs 195 ms in the organized atrial electrograms, 162 ms vs 163 ms in the disorganized atrial electrograms). However, each coefficient R at the peak AFCL from the signals with a low-pass filter was higher than that from the signals without a low-pass filter (0.64 vs 0.43 in the organized atrial electrograms, 0.42 vs 0.22 in the disorganized atrial electrograms).

*Signal Processing in the Spectral Analysis*

*Rectified Signals* It was difficult to identify the DF and peak AFCL when raw atrial electrograms were used (Fig 2). Thus, in this study, 75 segmental pieces of 30-s data were rectified according to the methods of previous reports.[16]

*Window for the FFT Analysis* Each DF performed with a Hamming window was equal to each DF performed with a Hanning window, using the rectified and low-pass (cutoff 20 Hz) filtered 30-s signals of AF (Fig 5). In all data (n=75), there was no difference in the DF of the FFT analysis performed with a Hamming window and that with a Hanning window (Table 1). Thus, no matter what signals were used for the DF in the FFT analysis, they were performed with a Hamming or Hanning window.

*Low-Pass Filter* In all data (n=75), we compared each DF of the FFT analysis performed with a Hamming window, using first the rectified and then the with and without low-pass filtered (cutoff 20 Hz) 30-s signals of AF (Table 2). No matter what signals were used for the DF in the FFT analysis, they were filtered with a low-pass filter. In the ACF analysis, the signals filtered with a low-pass filter did not significantly change the peak AFCL (5.70±1.05 Hz to 5.72±1.05 Hz), but significantly ($p<0.0001$) increased the coefficient R (0.22±0.09 to 0.41±0.15) (Table 2).

*Spectral Resolution of the FFT* In all data (n=75), we compared the DF of the 1,024-point, 2,048-point, 4,096-point and 8,192-point FFT analyses with a Hamming window using the rectified and then low-pass (cutoff 20 Hz) filtered 30-s signals of AF (Table 3). The DF was naturally influenced by the spectral resolution, but there was no significant difference.

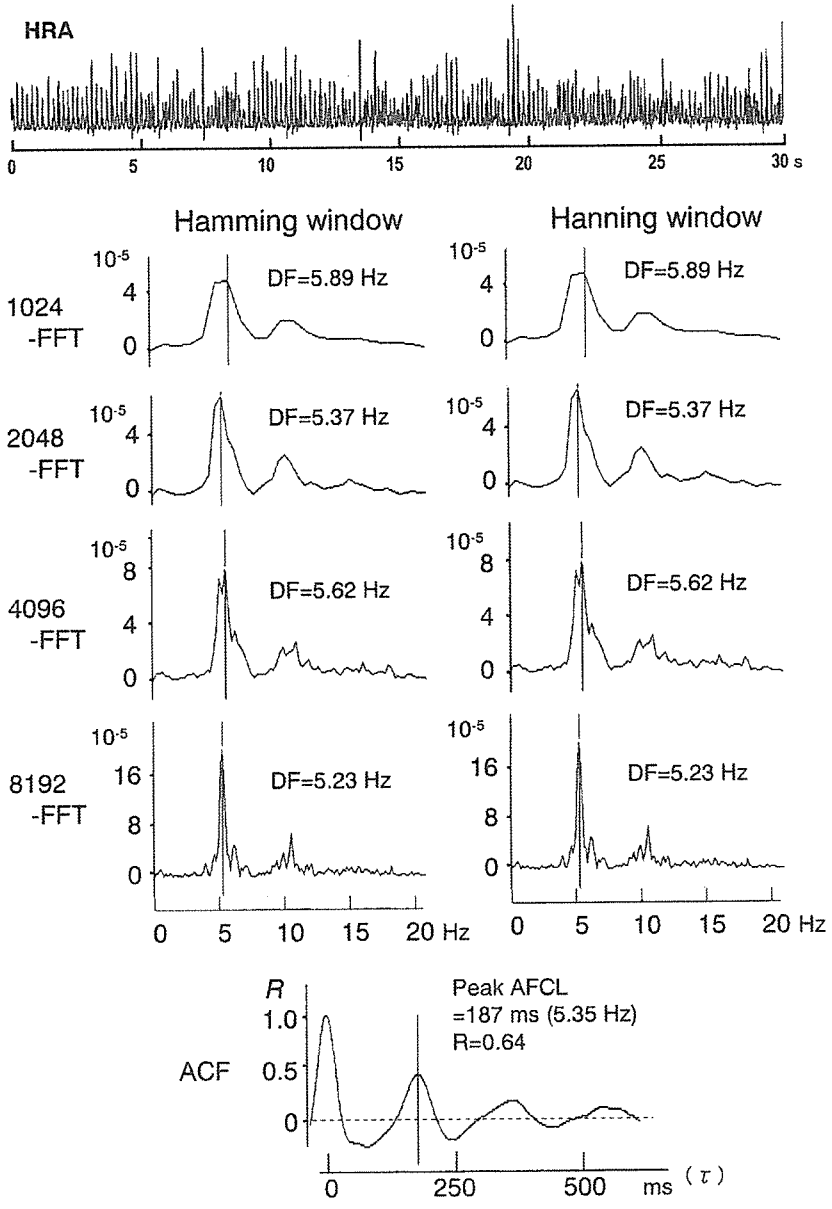


Fig 5. The 30-s rectified, and then low-pass filtered (20 Hz), atrial electrograms from the HRA with their corresponding FFT analyses performed with a Hamming window (Left panel) and with a Hanning window (Right panel), and ACF (Bottom panel). The 30-s data are the same as in Fig 1. HRA, high right atrium; FFT, fast Fourier transformation; DF, dominant frequency; ACF, autocorrelation function; peak AFCL, peak atrial fibrillation cycle length obtained from the ACF.

**Table 1 Dominant Frequency in Each FFT Analysis Performed With Either a Hamming or Hanning Window, Using the Rectified and Then Low-Pass (Cutoff 20 Hz) Filtered 30-s Signals of AF**

| | *1,024-point FFT* | *2,048-point FFT* | *4,096-point FFT* | *8,192-point FFT* |
|---|---|---|---|---|
| *Spectral resolution (Hz)* | *0.98* | *0.49* | *0.24* | *0.12* |
| *Hamming window* | *5.65±1.45* | *5.81±1.34* | *5.78±1.15* | *5.79±1.12* |
| *Hanning window* | *5.65±1.45* | *5.81±1.34* | *5.78±1.15* | *5.79±1.12* |

*FFT, fast Fourier transformation; AF, atrial fibrillation.*

**Table 2 Dominant Frequency in Each FFT Analysis Performed With a Hamming Window and the Peak AFCL in Each ACF, Using Rectified, With and Without Low-Pass (Cutoff 20 Hz) Filtering, 30-s Signals of AF**

| | *1,024-point FFT* | *2,048-point FFT* | *4,096-point FFT* | *8,192-point FFT* | *ACF* | |
|---|---|---|---|---|---|---|
| | | | | | *Peak AFCL (Hz)* | *Rxx (R)* |
| *Spectral resolution (Hz)* | *0.98* | *0.49* | *0.24* | *0.12* | | |
| *Low-pass filter (–)* | *5.65±1.45* | *5.81±1.34* | *5.78±1.15* | *5.79±1.12* | *5.70±1.05* | *0.22±0.09* |
| *Low-pass filter (+)* | *5.65±1.45* | *5.81±1.34* | *5.78±1.15* | *5.79±1.12* | *5.72±1.05* | *0.41±0.15* |

*AFCL, AF cycle lengths; ACF, autocorrelation function; Low-pass filter, filter set at 20 Hz. Other abbreviations see in Table 1.*

**Table 3 Dominant Frequency in Each FFT Analysis and Peak AFCL in Each ACF, Using the Rectified and Then Low-Pass (Cutoff 20 Hz) Filtered 30-s Signals of AF**

| | *1,024-point FFT (Hz)* | *2,048-point FFT (Hz)* | *4,096-point FFT (Hz)* | *8,192-point FFT (Hz)* | *Peak AFCL (Hz)* |
|---|---|---|---|---|---|
| *Spectral resolution (Hz)* | *0.98* | *0.49* | *0.24* | *0.12* | |
| *All (n=75)* | *5.65±1.45* | *5.81±1.34* | *5.78±1.15* | *5.79±1.12* | *5.72±1.05* |
| *Difference to the ACF* | *0.50±0.75* | *0.29±0.66* | *0.22±0.17* | *0.27±0.24* | – |
| *Induced group (n=40)* | *5.32±1.15* | *5.35±1.10* | *5.34±1.14* | *5.38±1.08* | *5.38±1.05* |
| *Persistent group (n=35)* | *6.03±1.67* | *6.33±1.42* | *6.28±0.94* | *6.26±0.10* | *6.12±0.91* |
| *Induced vs persistent* | *p=0.034* | *p=0.0012* | *p=0.0002* | *p=0.0005* | *p=0.0019* |
| *HRA (n=38)* | *5.70±1.66* | *5.93±1.53* | *5.81±1.20* | *5.79±1.15* | *5.75±1.10* |
| *LRA (n=37)* | *5.60±1.47* | *5.69±1.13* | *5.74±1.10* | *5.80±1.10* | *5.70±1.02* |
| *HRA vs LRA* | *p=0.752* | *p=0.442* | *p=0.798* | *p=0.966* | *p=0.853* |

*HRA, high right atrium; LRA, low lateral atrium. Other abbreviations see in Tables 1,2.*

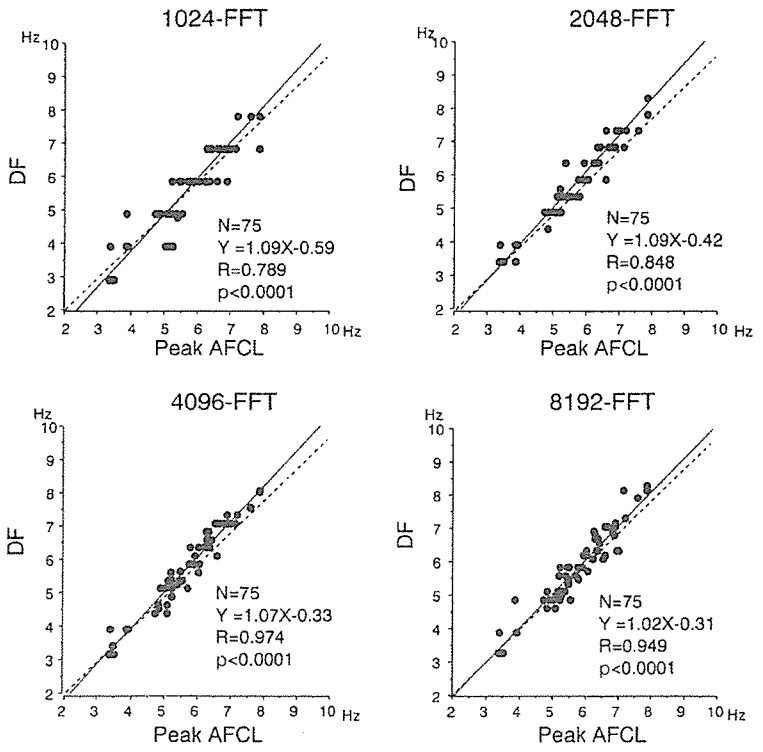


Fig 6. Relationship between the dominant frequency for each FFT and peak AFCL. The X axis indicates the peak AFCL and Y axis the dominant frequency. The peak AFCLs (ms) are expressed as Hz. The dominant frequency in the 4,096-point FFT analysis had the strongest relationship to the peak AFCL in the autocorrelation function. FFT, fast Fourier transformation; DF, dominant frequency; peak AFCL, peak atrial fibrillation cycle length obtained from the autocorrelation function.

*Relationship Between the DF and Peak AFCL*

In all data (n=75), there was a significantly ($p<0.0001$) strong relationship between the DF for each spectral resolution and peak AFCL (Fig 6). As shown in Fig 6, the intervals between the points of the DFs (in the vertical direction) depended on the spectral resolution of the FFT analysis. The intervals between the points of the DFs in the 1,024- and 2,048-point FFT analyses (spectral resolution 0.98 Hz and 0.49 Hz, respectively) were relatively larger than those in the 4,096-and 8,192-FFT analyses (spectral resolution 0.24 Hz and 0.12 Hz, respectively). The difference in the DF and peak AFCL was 0.50±0.75 Hz in the 1,024-point FFT, 0.29±0.66 Hz in the 2,048-point FFT, 0.22±0.17 Hz in the 4,096-point FFT and 0.27±0.24 Hz in the 8,092-point FFT. The DF in the 4,096-point FFT analysis had the strongest relationship with the peak AFCL (Fig 6) and also had the smallest difference (0.22±0.17 Hz), which was almost the same as the spectral resolution of the 4,096-point FFT analysis (0.24 Hz; Table 3).

When comparing the induced and persistent groups, the DF and peak AFCL in the induced group were significantly smaller than those in the persistent group (Table 3). Statistically, the p-value (=0.0002) for the 4,096-point FFT analysis was the smallest and that (=0.034) for the 1,024-point FFT analysis was the largest, but less than 0.05. When comparing the HRA and LRA, there was no significant difference in the DF or peak AFCL (Table 3).

*Influence of the Length of the AF Data Analyzed on the DF and Peak AFCL*

In the arbitrarily selected data (n=10), there was a significantly ($p<0.0001$) strong relationship between the DF and peak AFCL for each length of data analyzed (ie, 5, 10, 30 (30-s I) and 32.8 s; Table 4). The difference between the DF and peak AFCL was 0.40±0.37 Hz for the 5-s data, 0.31±0.25 Hz for the 10-s data, 0.19±0.14 Hz for the 30-s I and 0.20±0.12 Hz for the 32.8-s data. There was no significant difference in the difference between the DF and peak AFCL for the length of AF data analyzed.

There was a significantly ($p<0.0001$) strong relationship

**Table 4 Correlation and Difference Between the DF and Peak AFCL in Each Length of AF Data Analyzed by FFT and ACF**

| | Length of data (s) | | | | |
|---|---|---|---|---|---|
| | 5 | 10 | 30-I | 30-II | 32.8 |
| DF in the FFT* (Hz) | 6.03±1.43 | 6.15±1.30 | 5.83±1.26 | 5.98±1.33 | 5.83±1.26 |
| Peak AFCL in the ACF (Hz) | 5.83±1.22 | 5.94±1.23 | 5.86±1.23 | 5.86±1.23 | 5.87±1.25 |
| Difference between the DF and peak AFCL (Hz) | 0.40±0.37 | 0.31±0.25 | 0.19±0.14 | 0.20±0.15 | 0.20±0.12 |
| Correlation between the DF and peak AFCL (Hz) | y=0.8x+1.0, r=0.94, p<0.001 | y=0.91x+0.33, r=0.96, p<0.0001 | y=0.96x+0.28, r=0.98, p<0.0001 | y=0.96x+0.28, r=0.98, p<0.0001 | y=0.98x+0.18, r=0.98, p<0.0001 |

*FFT*, FFT point was 8,192 points for 5 s, 16,384 points for 10 s, 32,768 points for 30 s-I, 4,096 points for 30 s-II, and 32,768 points for 32.8 s. DF, dominant frequency. Other abbreviations see in Tables 1–3.*

between the DF and peak AFCL for the 30-s II data, and the difference between the DF and peak AFCL was 0.20± 0.15 Hz (Table 4). Further, in the comparison of the DFs for the 30-s I and 30-s II data (Fig 7), there was a significantly ($p<0.0001$) strong relationship ($y=1.03x-0.05$, $r=0.98$) and the difference between them was 0.24±0.24 Hz (Fig 7).

## Discussion

In humans, both assessment of the intervals from the atrial electrograms of intracardiac electrograms[8,16–19] and analysis of the surface electrograms[18] and their response to drugs have been performed. Furthermore, the AF intervals of intracardiac electrograms have been measured directly[5,18,20] and by frequency analysis[8–10,16,19] Manual measurement of the AF interval is very labor intensive and may include human bias. Thus, recently several methods for automatically measuring the AFCL have been developed[7–10,18,20] and of these, FFT is the most frequently used computerized technique[7,10,12–14]

*FFT Analysis*

In 1990, Karagueuzian et al[12] categorized AF into Wells classification[1] during acute AF in dogs. The FFT of the digitized electrograms (8–10 s, 800 Hz digitization) showed peaks mostly below 15 Hz (range 0–30 Hz) that were either discrete (narrow band) with clear harmonic components or had continuous (broad band) spectra, and which changed in a time- and site-dependent manner. Thus, the dynamics of AF were compatible with deterministic chaos, rather than with random dynamics[12]

When FFT analysis was performed on bipolar signals, the signal processing varied among the investigators[7,10,13,14,21] Ballmann et al[7] subjected the intraatrial recordings to FFT using a Hamming window and a 1,024-point discrete FFT (spectral resolution, 0.98 Hz). Lazar et al[14] recorded bipolar signals from the PV ostium; 2,048-point FFT (spectral resolution, 0.49 Hz) was performed for each successive 2-s segment recorded. Sanders et al[10] evaluated the feasibility of spectral analysis and DF mapping in patients with AF. The signals were tapered at their edges to a 0 value by a Hanning window, rectified, and processed with a nonbiased 3- to 15-Hz band-pass filter. A 4,096-point FFT (spectral resolution, 0.24 Hz) was used to obtain the power spectrum of the electrogram at each recording site[10,21] Mansour et al[13] performed FFT on optical and bipolar electrode recordings. Bipolar atrial electrograms were acquired at 1,000 Hz for 10 s and filtered (band pass 0.5–500 Hz), providing a spectral resolution of 0.1 Hz over a range of 0.4–60 Hz.

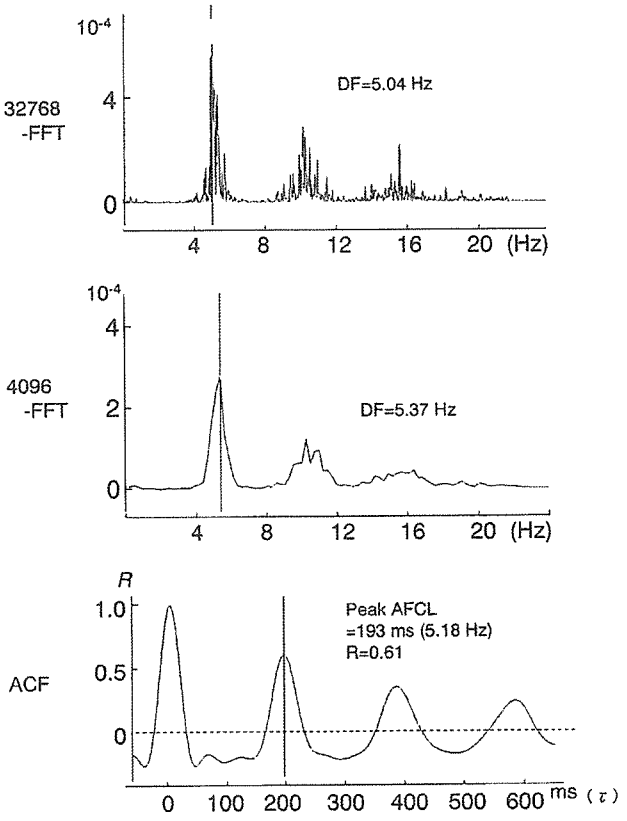


Fig 7. The 30-s rectified, and then low pass filtered (20 Hz), atrial electrograms from the HRA with 32,768-point FFT (Upper panel) and 4,096-point FFT (Middle panel) analyses performed with a Hamming window; and ACF (Bottom panel). FFT, fast Fourier transformation; DF, dominant frequency; ACF, autocorrelation function; peak AFCL, peak atrial fibrillation cycle length obtained from the ACF.

*Signal Processing in Spectral Analysis*

In the present study it was very difficult to identify the DF and peak AFCL when the raw atrial electrograms were used (Fig 2). Therefore, bipolar signals filtered with a band pass of 30–400 Hz must be rectified to identify the DF and peak AFCL for the measurement of the AFCL, as previously reported[10,14]

Low-pass (cutoff 20 Hz) filtering had been used to remove high-frequency potentials[6,14,15] which leaves a smoothed signal with peaks at the time of the local electrical activation (Fig 4). The filter cutoff values chosen were physiologically reasonable because it is unexpected for local atrial activation to occur at a rate faster than 20 Hz (50-ms cycle length) in human subjects[14,15] We studied the

DFs in 1,024-, 2,048-, 4,096- and 8,192-point FFT analyses using filtered (band pass 0.3–500 Hz), rectified, and then low-pass filtered 30-s signals of AF (Fig 5). However, the DF was not influenced when signals were filtered with the low-pass filter, although that significantly increased the coefficient R in the ACF.

A Hamming window[7] or Hanning window[10] was used when FFT analysis was performed. When the data were limited to the range handled in this study, the DF was not influenced by how the signals were tapered by the Hamming or Hanning window (Figs 3,4).

*ACF Analysis*

We developed an analysis of the AFCL using ACF analysis,[16] which is a measure of the time-related properties of data that are separated by fixed time delays. It can be estimated by delaying the recording relative to itself by some fixed time delay, $t$, then multiplying the original recording with the delayed recording, and averaging the resulting product values over the available recording length or over some desired portion of that recording length. The procedure is repeated for all time delays of interest.[22] In our method, each set of rectified atrial electrogram data was finally processed to obtain an autocorrelogram using a personal computer and BIMUTAS II for Windows software. The value of the first peak of the coefficient R, on the positive side of the autocorrelogram, was taken as the peak AFCL.[16] The first positive autocorrelogram crossing the baseline from negative to positive was taken as the minimum AFCL. In type I AF, the peak AFCL measured by the ACF method had a good correlation ($r=0.995$, $p<0.0001$) to the mean AFCL obtained by the computer-picked activation time method.[16]

*Comparison of the Organized and Disorganized Atrial Electrograms*

On the base of our demonstrations (Figs 3,4), each DF in the disorganized atrial electrograms was higher than that in the organized atrial electrograms. On the other hand, each peak AFCL in the disorganized atrial electrograms was less than that in the organized atrial electrograms. Both the power spectral density and the coefficient R in the disorganized atrial electrograms were less than those in the organized atrial electrograms.

*Relationship Between FFT and ACF*

When comparing the induced and persistent groups, the DF and peak AFCL in the induced group were significantly smaller than those in the persistent group (Table 3), as previously reported.[4] Statistically, the p-value (0.034) for the 1,024-point FFT analysis was the largest, but less than 0.05. As shown in Fig 6, the intervals between the points of the DFs (in the vertical direction) depended on the spectral resolution of the FFT analysis. The intervals between the points of the DFs in the 1,024- and 2,048-point FFT analyses (spectral resolution 0.98 H and 0.49 Hz, respectively) were relatively larger than those in the 4,096- and 8,192-point FFT analyses (spectral resolution 0.24 Hz and 0.12 Hz, respectively). These results suggest that the 1,024-point FFT analysis was not better for determining the AFCL. Because a gold-standard method for measuring AF intervals, especially type II or III AF, does not exist yet, no one can determine the best spectral resolution of FFT analysis for identifying the AFCL. It is believed that the DFs from the 2,048-, 4,096- and 8,192-point FFT analyses and peak AFCL from the ACF are useful for determining the AFCL. Furthermore, the ACF is supposed to have the possibility of giving further information on the AFCL, such as the minimum AFCL.[16]

There was a significantly ($p<0.0001$) strong relationship between the DF for each spectral resolution of the FFT analysis and peak AFCL (Fig 6). The difference in the DF from the 4,096-point FFT and peak AFCL was close to the spectral resolution of the 4,096-point FFT. Further, the relationship between the Hz and CL was similar to the relationship between the beats per minute and CL; for example, the DF range from 5 to 6 Hz was the same as the CL that ranged from 200 ms to 167 ms, with a difference of 33 ms. The DF range from 7 to 8 Hz was the same as the CL that ranged from 143 ms to 125 ms, with a difference of 18 ms. Thus, the larger the Hz the smaller the difference in the CL.

*Influence of the Length of Analyzed Data on the DF and Peak AFCL*

The length of the data analyzed should influence the FFT and ACF analyses. In particular, in this study the ACF was computed by taking the inverse Fourier transformation of the autospectrum estimate using BIMUTAS II. The number of $2^n$, which was greater than the number of points analyzed, was selected as the FFT point. On the other hand, the signal-averaging process was performed when the length of the AF data analyzed exceeded the FFT point in the FFT analysis. These facts indicate that the length of the AF data actually analyzed in the spectral analysis was restricted by both the FFT point and the length of the AF data selected for the analysis. For example, when a 30-s AF data set was selected for the 4,096-point FFT, the signal-averaging was done in 7 segments and the 0-padding was performed for 1,328 points (=30,000–4,096×7). Thus, the length of the AF data actually analyzed in the FFT analysis was 28,630 ms. In the ACF with the 30-s AF data, 32,768-points were selected as the FFT point for the ACF, then 0-padding was performed for 2,768 points (=32,768–30,000). If the same length of AF data were chosen for the spectral analysis, the length of the AF data actually analyzed in the spectral analysis and FFT point (spectral resolution) were not the same in the FFT and ACF analyses. Naturally, the DF from the FFT analysis and peak AFCL from the ACF were not equal when using BIMUTAS II.

To compare the DF and peak AFCL obtained from the same FFT point (Table 4), we selected a 8,192-point FFT for the FFT analysis of the 5-s AF data, because when such data were analyzed the 8,192-point FFT was automatically selected by BIMUTAS II for the ACF analysis. Further, we similarly compared 10- and 30-s sets of data, and although the DF and peak AFCL had a strong correlation and small difference, they were not equal. We also compared both for the 32.8-s data to make the number of points for the 0-padding as small as possible. The DF and peak AFCL also had a strong correlation and small difference (Table 4), but were not equal, although mathematically they should have been equal. There is the possibility that there were some errors or differences in the signal processing for the ends of the data using BIMUTAS II. However, both the DF and peak AFCL had a strong correlation and small difference. The peak AFCL from the ACF analysis was not of the same quality, but had the same value as the DF from the FFT analysis.

Because the signal-averaging process was performed when the length of the AF data exceeded the selected FFT

point (spectral resolution), we compared the DF for the 30-s data using a 4,096-point FFT and 32,768-point FFT (30-s II in Table 4). Neither was naturally equal because of the different spectral resolutions and different lengths of the AF data actually analyzed, but they had a strong correlation and small difference.

*Study Limitations*

The major limitation is that the ACF was computed by taking the inverse Fourier transformation of the autospectrum estimate for the multipurpose analysis of biophysical information. Thus, the length of the AF data analyzed was restricted to the number of $2^n$. The number of $2^n$ that exceeded the number of analyzed points was automatically selected as the FFT point. Therefore, the results of this study might be limited using our methods.

Though the advantage of our method is that all the data from the electrograms stored on a hard disk from the EP-LAB (band pass filter 30–400 Hz) during the electrophysiological study were available for analysis, the atrial electrograms recorded with the band-pass filters produced an artificial wave in the atrial electrograms. Therefore, we used rectified atrial electrograms to diminish that issue. There is the possibility that the rectified atrial electrograms recorded with the band-pass filters may have influenced the results of the spectral analysis, although we have already proved the usefulness of our method for measuring the AFCL![6] When the recorded signals contained noise or were poor recordings, there was the possibility of misinterpreting them.

In summary, the DF from the FFT analysis and peak AFCL from the ACF had a strong correlation and small difference, when the same AF data and same duration were chosen using multipurpose analysis of biophysical information (BIMATSU II). When using the 30-s AF data, the peak AFCL from the ACF was the closest to the DF of the 4,096-point FFT analysis. The proper spectral resolution of the FFT analysis depends on the purpose of the study. When the purpose of the study is the measurement of the AFCL, the peak AFCL is not of the same quality, but has the same value as the DF from the FFT analysis.

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*Circ J* 2007; **71:** 271–275

# Rationale and Design for a Study Using Intravascular Ultrasound to Evaluate Effects of Rosuvastatin on Coronary Artery Atheroma in Japanese Subjects

## —— COSMOS Study (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) ——

Tadateru Takayama, MD; Takafumi Hiro, MD*; Masakazu Yamagishi, MD**;
Hiroyuki Daida, MD†; Satoshi Saito, MD††;
Tetsu Yamaguchi, MD‡; Masunori Matsuzaki, MD*

**Background** There have been few multicenter studies using intravascular ultrasound (IVUS) to assess the process of atherosclerosis in a Japanese population with hypercholesterolemia that is being treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for control of low-density lipoprotein-cholesterol.
**Methods and Results** An open-label multicenter study is planned to evaluate with IVUS whether treatment with rosuvastatin for 76 weeks results in regression of coronary artery atheroma volume in patients who have coronary heart disease (CHD) and hypercholesterolemia. Sample size is 200 subjects with CHD who are to undergo percutaneous coronary intervention. The planned duration is between October 2005 and October 2008.
**Conclusions** The COSMOS study will be the first multicenter cardiovascular study in a Japanese population and may provide new evidence on the effects of rosuvastatin on the progression of coronary atherosclerotic lesions. (*Circ J* 2007; **71:** 271–275)

**Key Words:** Atherosclerosis; Coronary disease; Intravascular ultrasound; Lipids; Rosuvastatin

Coronary heart disease (CHD) is the single largest cause of death of men and women in many countries. The Framingham Heart Study identified total cholesterol (TC) as a major contributor to CHD and strongly related to progression of the disease[1,2] The National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) identified low-density lipoprotein (LDL)-cholesterol (C) as the primary target for cholesterol-lowering therapy to prevent CHD (NCEP ATP II 1993)[3] NCEP ATP III clinical updates include guidelines recommending intensive dietary and drug management of LDL-C in patients with CHD (ATP II) and more intensive LDL-lowering therapy for high-risk patients (ATP III) in order to achieve LDL-C levels <100 mg/dl [2.59 mmol/L] (NCEP ATP III 2001)[4] A high LDL-C level is recognized as an independent risk factor for CHD events and many guidelines therefore advocate LDL-C reduction. The Japan Lipid Intervention Trial (J-LIT), which is a national cohort study, showed that normalization of the lipid concentration reduced the risk of coronary events in 52,421 Japanese patients with hypercholesterolemia[5]

Statins are now the most widely used medication for the treatment of hypercholesterolemia because they partially inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting step in cholesterol synthesis. HMG-CoA reductase inhibition consequently induces the compensatory upregulation of hepatic LDL receptors, which enhances the LDL-C uptake and results in a decrease in the plasma concentration of LDL-C. It has been well recognized that statins are associated not only with reduction of LDL-C levels but also with substantial reduction of the prevalence of coronary events. Clinical trials have confirmed that these agents reduce coronary events in subjects with and without coronary disease, reduce cardiovascular morbidity and mortality, and may even promote regression of atherosclerotic vascular lesions[6–10] The benefits of statin therapy on primary and secondary prevention in patients with a wide range of LDL-C levels is therefore well established. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)[11] and Treat to New Targets (TNT)[12] studies showed that intensive lipid-lowering therapy significantly reduces the risk of cardiovascular disease events compared with moderate lipid-lowering therapy (p=0.005 and p<0.001, respectively). These studies

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*Division of Cardiovascular Medicine, Department of Medicine, Nihon University School of Medicine, Tokyo, *Division of Cardiology Medicine, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, **Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa, †Department of Cardiology, Juntendo University School of Medicine, ††Department of Advanced Medicine, Nihon University School of Medicine and ‡Cardiovascular Center, Toranomon Hospital, Tokyo, Japan*
Mailing address: Satoshi Saito, MD, Department of Advanced Medicine, Nihon University School of Medicine, 30-1 Ohyaguchikami-cho, Itabashi-ku, Tokyo 173-8610, Japan. E-mail: satoshis@med.nihon-u.ac.jp

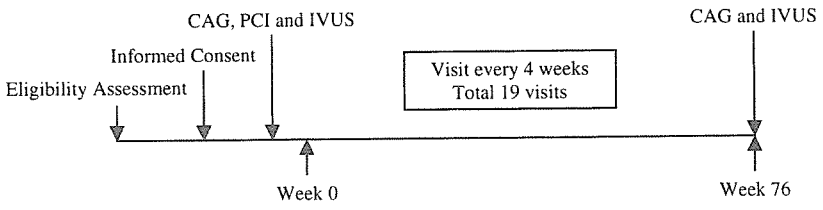


Fig 1. Flow chart showing the study timeline. CAG, coronary angiography; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

would suggest that very intensive lipid lowering is required to induce regression of atherosclerosis.

The ability of statins to reduce progression of coronary atherosclerosis or to induce its regression has been evaluated by coronary angiography in a number of studies: MARS[13] CCAIT[14] The Multicenter Anti-Atheroma study (MAAS Investigators 1994), and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I)[15] However, almost all the angiographic studies have revealed that the change in luminal parameters, such as the percent diameter stenosis and the minimal lumen diameter, was very subtle, although it was statistically significant. It was partially the vessel remodeling that masked the net change of plaque volume, and therefore, it has been recognized that direct plaque imaging might be more useful for assessing the effect of lipid-lowering drugs on the process of atherosclerosis.

Intravascular ultrasound (IVUS) is a modality that quantitatively represents atherosclerosis in vivo. IVUS enables accurate measurement of the lumen area, as well as atheroma size and distribution. The REVERSAL trial[16] (Reversal of Atherosclerosis with Aggressive Lipid Lowering) and ASTEROID trial[17] (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) have successfully investigated the effects of statins on atherosclerosis. Most particularly, ASTEROID is the first study to clearly show a reversal of the atherosclerotic disease process in major clinical studies. This was a 24-month single-arm, blinded endpoint, multinational study conducted in 9 countries: Australia, Belgium, Canada, France, Italy, Netherlands, Spain, the United Kingdom, and the United States of America. For the primary efficacy parameter of the percentage atheroma volume, the median was –0.79% (97.5% confidence interval (CI), –1.21% to –0.53%) ($p<0.001$ compared with baseline). This was accomplished with rosuvastatin 40 mg/day, and reduced LDL-C by 53.2% and increased high-density lipoprotein (HDL)-C by 14.7%. Rosuvastatin is the most effective of the new generation statins, and should enable more patients to achieve lipid goals with the starting dose![18]

In Japan, however, the beneficial effect of statin treatment on atherosclerotic lesions for 6 months after a coronary event was shown in the small, single-center, ESTABLISH Study![19] The subjects were randomized to atorvastatin (intensive lipid-lowering therapy) or control groups after percutaneous coronary intervention (PCI). LDL-C was significantly reduced by 41.7% in the atorvastatin group compared with an increase of 0.7% in the control group ($p<0.001$). Plaque volume was significantly reduced in the atorvastatin group (13.1±12.8% decrease) compared with the control group (8.7±14.9% increase; $p<0.0001$), even in patients with low baseline LDL-C (<125 mg/dl).

Based on a linear relationship identified between the decrease in LDL-C and the change in the luminal diameter of the coronary artery, it was suggested that at least 40% reduction in LDL-C is needed to arrest progression of the atherosclerotic process?[20] Birgelen et al[21] reported possible suppression of progression of plaque (area) at LDL-C levels of <75 mg/dl. The ASTEROID trial suggested that treatment to LDL-C levels below currently accepted guidelines, such as NCEP ATP III and the Third Joint Task Force European guidelines, when accompanied by significant HDL-C increase, could produce regression of atherosclerosis in coronary disease patients. Recently, a meta-analysis has demonstrated that the pleiotropic effects of statins do not seem to contribute an additional cardiovascular risk reduction benefit beyond that expected from the degree of LDL-C lowering?[22] Therefore, there might be a fundamental 1-to-1 relationship between LDL-C levels and CHD events. However, the most relevant parameter to provoke significant change of plaque volume, especially for the Japanese, is still unknown: an absolute level of LDL-C or the magnitude of change in LDL-C?

## COSMOS Study

The COSMOS study will be the first multicenter study especially in a Japanese population to evaluate the effects of rosuvastatin on regression of coronary atherosclerosis. Comparisons will be made between the measurements of atherosclerosis at the beginning vs the end of drug treatment. This study is a single-arm study. As placebo controlled trials of statins in this population are no longer ethically acceptable, a comparator group receiving either placebo or a less active statin will not be included in the COSMOS study. Moreover, current US and EU guidelines also recommend achieving more intensive target levels in very high-risk, secondary-prevention patients?[23] IVUS was selected to evaluate coronary artery atheroma volume as the primary endpoint because of the high sensitivity of this imaging method compared to coronary angiography (CAG).

The COSMOS study will provide new evidence and therapeutic standards for the prevention of CHD in Japan by controlling LDL-C levels with rosuvastatin.

*Study Design*

This will be a 76-week, open-label, multicenter study to evaluate the effect of rosuvastatin on coronary artery atheroma volume as measured by IVUS in patients with CHD.

Eligible patients will begin treatment with rosuvastatin 2.5 mg once daily. The dosage will be increased by titration within the usual dose range with a treatment goal of lowering LDL-C below 80 mg/dl based on safety and the relationship between suppression of coronary artery plaque progression and LDL-C level in prior studies![11,15,16,19,21] If LDL-C levels are still 80 mg/dl or above after 4 weeks of treatment, the dosage may be increased up to a maximum of 20 mg/day. If the investigator finds it necessary to reduce the dosage because of an excessive decrease in LDL-C (<50 mg/dl) or occurrence of adverse events, the dosage may be reduced again to the starting dose of 2.5 mg once

daily.

A total of 19 scheduled visits are planned during the course of this study. Subjects will attend follow-up visits every 4 weeks over 76 weeks after starting the treatment with rosuvastatin. IVUS and CAG will be performed at baseline and Week 76.

Prior to any study-related activities, all subjects will sign an informed consent form. This study is approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all of the participating centers (Fig 1). The planned duration is between October 2005 and October 2008.

*Patient Population*

All patients have to meet all of the inclusion criteria: aged 20–75 years undergoing CAG or PCI; serum cholesterol level either (a) untreated patients: LDL-C ≥140 mg/dl [calculated with Friedewald equation (triglyceride (TG) <400 mg/dl) or directly measured] or TC ≥220 mg/dl, or (b) patients already treated with lipid-lowering agents: LDL-C ≥100 mg/dl [calculated with Friedewald equation (TG <400 mg/dl) or directly measured] or TC ≥180 mg/dl; the patient must have at least 1 significant stenosis of 75% or more and be a candidate for PCI, and in addition to the candidate lesion for PCI, there must be at least 1 lesion ≤50% stenosis that can be imaged by IVUS.

Exclusion criteria are: (1) acute myocardial infarction within 72 h of the onset of the study, (2) heart failure of New York Heart Association class III or IV, (3) secondary hyperlipidemia, (4) administration of cyclosporine, (5) hemodialysis, (6) lesions requiring intervention, (7) left main coronary artery disease of >50% stenosis, (8) uncontrolled hypertension (diastolic blood pressure ≥110 mmHg or systolic blood pressure ≥200 mmHg for all measurements during the screening period), (9) uncontrolled diabetes (hemoglobin A1c ≥9.5%), (10) active liver disease or liver dysfunction with ≥2.5×ULN (upper limit of the normal) of either alanine aminotransferase, aspartase aminotransferase or alkaline phosphatase, or ≥3.0 mg/dl of total bilirubin, (11) creatinine clearance <30 ml/min or serum creatinine >2.0 mg/dl, (12) serum creatine kinase >3×ULN, (13) short plaque lesions with a length less than 6 mm.

*IVUS Examination*

IVUS will be used to examine lumen area, atheroma size and distribution at baseline and after 76 weeks of treatment. Investigators will be required to use the same imaging system with the same type of IVUS catheter for both the baseline and follow-up examinations: Clearview®, Galaxy™ ultrasound system or Galaxy2™ ultrasound system with the Atlantis™ SR Pro 2 40 MHz imaging catheter (Boston Scientific, Natick, MA, USA). The images will be optimized under visual inspection by manipulating the system settings. The gain settings will be determined with the intention of maximizing image morphology without excessive dropout, not saturating adventitial intensity, and minimizing noise. The automated pullback device will be set with a speed of 0.5 mm/s. IVUS images will be recorded on super-VHS (S-VHS) videotapes or Digital Video Disk plus Re-Writable (DVD+RW) disk. The images will be logged and analyzed blind by 2 experienced technicians in the core lab.

*IVUS Analysis*

Plaque volume will be assessed by volumetric analysis with the echoPlaque2 system (Indec Systems Inc). Baseline and follow-up IVUS images will be reviewed side-by-side on a display, and the target segment selected. The target segment to be monitored will be determined in a non-PCI site (>5 mm proximal or distal to the PCI site) with a reproducible index such as side branches, calcifications, or stent edges.

*Endpoints*

The primary endpoint is the percent change in the plaque atheroma volume (target lesion length measured will be a minimum of 6 mm) from baseline to Week 76.

The secondary endpoints are actual volume changes and percentage changes in plaque area, in the vascular cross-sectional lumen area and total vascular area from baseline to Week 76 at the same preselected coronary artery cross-section.

Percent changes from baseline to specified measurement time points in TC, LDL-C, very LDL-C (VLDL-C), HDL-C, non-HDL-C (TC-HDL-C), TG and remnant like particle (RLP-C), apoprotein (Apo)A-I, ApoA-II, ApoB, lipoprotein (a) (Lp(a)), small dense LDL, HDL-2 and HDL-3 will also be calculated.

Changes in high sensitivity C-reactive protein from baseline to specified measurement time points will be calculated. RLP-C will be measured by the immunity adsorption method and ApoA-I, ApoA-II and ApoB by turbidimetric immunoassay. Lp(a) will be measured by latex-enhanced turbidimetric immunoassay and small dense LDL, HDL-2 and HDL-3 by the ultracentrifugation method. All laboratory measurements will be performed at a central clinical laboratory (SRL, Inc, Tokyo, Japan).

*Safety*

Safety will be observed throughout the study. Adverse events, subjective symptoms/objective findings, body weight, resting 12-lead ECG, chest X-ray, general blood tests (hematology, renal and liver functions, glucose metabolism), urinalysis, and vital signs (blood pressure, pulse) will be observed.

*Sample Size*

In the protocol, the assumptions used for power calculations require a sample size of 126 patients to provide 80% power (assuming a SD of 24.9%) to detect a 6.3% difference in the primary endpoint with 2.5% type I error rate for a 1-sided test. It was therefore determined that the enrollment of 200 patients per treatment would provide an adequate number of patients.

*Analysis Population*

The primary analysis population for efficacy will comprise subjects who comply with the protocol and have IVUS data that can be evaluated at both baseline and Week 76. This analysis population is defined as a per-protocol set. A full analysis set, defined separately, will be used as the secondary analysis population.

*Efficacy Analysis*

The primary endpoint and secondary endpoints defined as percentage changes or changes from baseline will be summarized by mean, standard deviation, minimum, median and maximum, and then 95% CIs will be calculated. The null hypothesis that percentage change or change from baseline is equal to 0 is tested by 1-sample t-test.

*Safety Analysis*

For safety evaluation, the numbers and prevalence of adverse events (including abnormal changes in physical values and clinical laboratory values) and the prevalence of adverse drug reactions (adverse events to which causality of rosuvastatin cannot be ruled out) will be calculated. Adverse events and adverse drug reactions will be summarized by type, severity, causality and duration of event.

*Study Organization*

*Principal Investigator* Masunori Matsuzaki, Division of Cardiology Medicine, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan.

*Steering Committee* Tetsu Yamaguchi, Cardiovascular Center, Toranomon Hospital, Tokyo, Japan; Hiroyuki Daida, Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan.

*Core Laboratory* Satoshi Saito, Department of Advanced Medicine, Nihon University School of Medicine, Tokyo, Japan.

## Conclusion

The COSMOS study will be the first multicenter study performed in a Japanese population using IVUS to evaluate the effects of rosuvastatin on regression of coronary atherosclerosis. We hope to show that intensive LDL-C lowering by rosuvastatin reduces coronary artery atheroma volume from baseline in diseased coronary segments.

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## Appendix 1

*Investigators*

S Fujii, Department of Cardiovascular Medicine, Graduate School of Medicine, Hokkaido University, Sapporo; N Funayama, Department of Cardiology, Hokkaido Cardiovascular Hospital, Sapporo; H Atsumi, Department of Internal Medicine, Yamagata Prefectural Shinjo Hospital, Shinjo; T Kubota, Department of Cardiology, Saitama Cardiovascular and Respiratory Center, Ohsato; T Ohba, Department of Internal Medicine, Chiba Hokusoh Hospital, Inba; T Takayama, Division of Cardiovascular Medicine, Department of Medicine, Nihon University School of Medicine, Tokyo; K Miyauchi, Department of Cardiology, Juntendo University School of Medicine, Tokyo; S Tani, Department of Cardiology, Nihon University Surugadai Hospital, Tokyo; S Ishiwata, Department of Cardiology, Cardiovascular Center, Toranomon Hospital, Tokyo; K Fukui, Department of Cardiovascular Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama; T Matsushita, Department of Cardiovascular Medicine, Aichi Prefectural Cardiovascular and Respiratory Center, Ichinomiya; T Kondo, Department of Cardiology, Komaki City Hospital,

Komaki; K Nishigaki, Department of Internal Medicine II, Gifu University Hospital, Gifu; H Matsuo, Department of Cardiology, Gifu Prefectural Gifu Hospital, Gifu; K Ueno, Department of Cardiology, Gifu Municipal Hospital, Gifu; T Kimura, Department of Cardiovascular Medicine, Kyoto University Hospital, Kyoto; A Kawamura, Division of Cardiology, National Cardiovascular Center, Suita; N Awata, Department of Cardiology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; Y Kobayashi, Department of Internal Medicine and Cardiology, Osaka City University Medical School, Osaka; A Itoh, Department of Cardiology, Osaka City Central Hospital, Osaka; Y Nagai, Department of Cardiovascular Medicine, Rinku General Medical Center, Izumisano; Y Kihara, Department of Cardiovascular Medicine, Kobe General Hospital, Kobe; T Kawagoe, Department of Cardiovascular Medicine, Hiroshima Municipal Hospital, Hiroshima; T Hiro, Division of Cardiology Medicine, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube; H Ogawa, Division of Cardiology, Tokuyama Central Hospital, Shunan; T Kawasaki, Department of Cardiovascular Medicine, Shinkoga Hospital, Kurume; T Honda, Cardiovascular Center, Saiseikai Kumamoto Hospital, Kumamoto; M Nakamura, Department of Cardiology, Toho University Ohashi Medical Center, Tokyo; K Urasawa, Cardiovascular Center, Tokeidai Memorial Hospital, Sapporo; H Iida, Department of Cardiology, National Hospital Organization Hamada Medical Center, Hamada; S Ono, Department of Cardiology, Saiseikai Yamaguchi General Hospital, Yamaguchi; T Oda, Department of Cardiology, Shimane Prefectual Central Hospital, Izumo; S Minagoe, Department of Cardiology, National Hospital Organization Kagoshima Medical Center, Kagoshima; K Hibi, Cardiovascular Center, Yokohama City University Medical Center, Yokohama; N Kubo, Cardiovascular Division, Omiya Medical Center, Jichi Medical School, Saitama; Y Sakanoue, Department of Cardiology, Seichokai Fuchu Hospital, Izumi; M Kawashiri, Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa; H Shimomura, Division of Cardiology, Fukuoka Tokushukai Medical Center, Kasuga; T Fujita, Division of Cardiology, Sapporo-Higashi Tokushukai Medical Center, Sapporo; J Yajima, Department of Cardiology, The Cardiovascular Institute, Tokyo, Japan.

Review

# Statins: Beneficial or Adverse for Glucose Metabolism

Jun Sasaki[1], Mikio Iwashita[2], and Suminori Kono[2]

[1]Graduate School of Clinical Trial Management, International University of Health and Welfare, Fukuoka, Japan.
[2]Department of Preventive Medicine, Kyushu University Faculty of Medical Sciences, Fukuoka, Japan.

Large-scale clinical trials have established that statin use for lowering blood cholesterol is beneficial in reducing atherosclerotic cardiovascular diseases in different populations. However, the general reputation of statins seems to be clouded by a potential adverse effect of a class of statins on glucose metabolism. This paper reviewed clinical data of statins regarding the effects on diabetes mellitus and glucose metabolism. At least five randomized controlled studies, primarily investigating the protective effect of statins on the risk of cardiovascular diseases, have addressed the effect of statins on glucose metabolism in Western countries. One study showed that pravastatin (40 mg/day) was protective against the development of diabetes mellitus. Two studies of atorvastatin (10 mg/day) and one study of simvastatin (40 mg/day) showed no measurable effect of these regimens on the risk of diabetes mellitus or the clinical course of diabetes mellitus. One study of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) suggested a deterioration of glucose metabolism associated with a high dose of atorvastatin. In Japan, a few case reports have noted a potential adverse effect of atorvastatin on glycemic control in patients with diabetes mellitus; however, seven clinical trials have showed no such effect of atorvastatin although these studies were relatively small in size and short in follow-up. Only one of the two observational studies suggested a possible adverse effect of atorvastatin on glycemic control. Evidence is extremely limited regarding atorvastatin use and deterioration in glycemic control, and further studies are needed to draw a conclusion on this issue.

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**Key words;** Pravastatin, Atorvastatin, Diabetes mellitus, Insulin, Blood glucose

## Introduction

Statins, HMG-CoA reductase inhibitors, enhance the expression of low-density lipoprotein (LDL) receptors in the liver and consequently lower blood LDL cholesterol levels through inhibiting cholesterol synthesis in the liver[1]. From large-scale clinical trials in different populations[2-4], it has been established that statin use substantially reduces the risk of cardiovascular diseases. In addition to lowering LDL cholesterol levels, statins are known to suppress the progression of atherosclerosis by their pleiotropic effects including the improvement of thrombus formation, antioxidant effect, improvement of vascular endothelial cell damage, anti-inflammatory action, and stabilization of plaques[5]. Evidence from clinical trials has given statins the general reputation as very effective and safe cholesterol-lowering drugs, although adverse effects of statins, such as elevation of liver enzymes and rhabdomyolysis, are recognized. However, an incident of fatal rhabdomyolysis associated with cerivastatin raised a concern that the clinical efficacy and safety of statins may differ by the class of statins[6]. Differences in the structural and physical properties of statins might result in the variation in pharmacokinetics, pleiotropic effects, and drug interactions[5].

It has been a matter of recent concern whether atorvastatin deteriorates diabetes mellitus or glycemic control. In 2003, immediately after the introduction of atorvastatin, two independent groups each reported two cases of diabetes mellitus showing deterioration in

Address for correspondence: Jun Sasaki, Graduate School of Clinical Trial Management, International University of Health and Welfare, 1-3-1 Nagahama, Chuo-ku, Fukuoka 810-0072, Japan.
E-mail: jsas@nifty.com
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**Table 1.** Atorvastatin use and deterioration of blood glucose status in patients with diabetes mellitus: case reports presented at recent meetings in Japan

| Authors | Main findings | Reference |
|---|---|---|
| Nunoi, et al. | Deteriorated HbA1c with ATR for 2 months (2 cases). | J Jpn Diab Soc, 46: 202, 2003 |
| Murakami, et al. | Deteriorated FBS with ATR 5 mg for 3 M and 10 mg for 2 months (2 cases). | J Cardiol, 42 (Suppl 1): S455, 2003 |
| Katoh, et al. | Deteriorated HbA1c with ATR 5 mg for 1 month and with ATR 10 mg for 4 months (2 cases). | J Jpn Diab Soc, 48: 71, 2005 |
| Kodera, et al. | Deteriorated non-fasting BS/HbA1c with ATR for 3-4 months (2 cases) | J Jpn Diab Soc, 48: 392, 2005 |
| Seguchi, et al. | Deteriorated FBS/HbA1c with ATR for 3-6 months (3 cases) | J Jpn Diab Soc, 48: 392, 2005 |
| Fukuniwa, et al. | Deteriorated HbA1c with ATR 5 mg for 2 months and then with PRV 10 mg for 2 months (1 case) | J Jpn Diab Soc, 48: 451, 2005 |

ATR: atorvastatin, BS: blood sugar, FBS: fasting blood sugar, PRV: pravastatin.
Based on the Japan Medical Abstracts Society web version 3 with a combination of key words (HMG-CoA reductase inhibitors, diabetes mellitus, proceedings, and human).

glycemic control during treatment with atorvastatin, and at least eight such cases were reported subsequently at meetings in Japan (**Table 1**). Very recently, a case of type 2 diabetes mellitus occurring after atorvastatin treatment was published[7]. In this case, however, hyperglycemia, which was resolved with insulin therapy and discontinuation of atorvastatin, recurred with pravastatin use. As discussed in detail below, a substudy of a multicenter randomized controlled trial, which was presented at the 2004 meeting of the American Heart Association (AHA), suggested that a high dose of atorvastatin (80 mg/day) might deteriorate glycemic control[8]. In this paper, we review clinical data concerning the effects of statins on glucose metabolism, especially from the safety aspect, and discuss the possible mechanisms of these effects. For this task, we searched for relevant articles in PubMed with the combination of "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[MeSH], "Clinical Trials"[MeSH] and "Diabetes Mellitus"[MeSH], and also the Japan Medical Abstracts Society web version 3 with a combination of key words (HMG-CoA reductase inhibitors, diabetes mellitus, original article/proceedings, and human). The search was limited to publications in the year 2000 and thereafter, and was done on January 10, 2006. Related articles were also searched for by scanning the references quoted in the articles at hand.

## Randomized Controlled Trials in Western Countries

The effects of statins on the risk of diabetes mellitus or glycemic control have been directly addressed in at least five randomized controlled trials with the event of cardiovascular diseases as the primary endpoint. The West of Scotland Coronary Prevention Study[9] was the first clinical trial which investigated the risk of diabetes mellitus associated with statin treatment. Originally, it was a double-blind trial in which 6,595 men aged 45-64 years with hypercholesterolemia but no evidence of cardiovascular disease were randomized to receive either pravastatin (40 mg/day) or placebo treatment[3]. The subjects in the substudy were 5,974 men who had two or more post-randomization measurements of blood glucose and had neither self-reported diabetes nor fasting blood glucose of $\geq$ 7.0 mmol/L at baseline. The incidence of diabetes mellitus was defined as two glucose measurements of $\geq$ 7.0 mmol/L and at least one measurement of $\geq$ 2.0 mmol/L above the baseline level or newly started prescription of hypoglycemic drugs. During the follow-up period of 3.5-6.1 years, 139 became diabetic. After adjustment for body mass index, triglyceride, blood glucose, and other characteristics at baseline, the patients assigned to pravastatin therapy had a hazard ratio of 0.70 (95% confidence interval, 0.50-0.98) for transition to diabetes mellitus[9].

In the MRC/BHF Heart Protection Study[10], 20,536 subjects aged 40 to 80 years with and without diabetes mellitus were randomized to receive either simvastatin (40 mg/day) or placebo. The mean duration of follow-up was 4.8 years for participants with diabetes mellitus at entry and 5.0 years for those without. Among the 14,573 subjects without known diabetes mellitus at baseline, there was no difference in the incidence of diabetes mellitus defined as the initiation of oral hypoglycemic or insulin treatment or a specific report of new diabetes mellitus (4.6% in the simvastatin group and 4.0% in the placebo group, $p=0.10$)[11]. Furthermore, among a random sample of 1,087 patients with diabetes mellitus at baseline, HbA1c levels slightly increased in both simvastatin (0.15%) and placebo (0.12%) groups during the study period, with no measurable difference between the

two ($p=0.8$)[11].

In the Anglo-Scandinavian Cardiac Outcomes Trial[12], 19,342 hypertensive patients aged 40 to 79 years were randomized to either of two antihypertensive regimens and 10,305 with non-fasting total cholesterol concentrations of 6.5 mmol/L or less were further randomized to either atorvastatin (10 mg/day) or placebo treatment. The median follow-up was 3.3 years. The occurrence of diabetes mellitus was prespecified as a tertiary endpoint. There was no difference in the development of diabetes mellitus between the atorvastatin and placebo treatments; the hazard ratio for atorvastatin versus placebo was 1.15 (95% confidence interval, 0.91 to 1.44).

In a substudy of the Pravastatin or Atorvastatin Evaluation in Myocardial Infarction (PROVE-IT) presented at the 2004 AHA meeting[8], the effects of the two statins on glycemic control were evaluated. PROVE-IT was the first large-scale clinical study comparing two statins[13]. In this study, 4,162 patients were randomized to receive intensive lipid-lowering therapy with atorvastatin (80 mg/day) or standard lipid-lowering therapy with pravastatin (40 mg/day) immediately after the occurrence of acute coronary syndrome. As compared with patients treated with pravastatin, those with atorvastain had a higher risk of developing HbA1c>6.0% among those with baseline HbA1c ≤ 6.0% regardless of diabetes mellitus; the pooled hazard ratio was estimated to be 1.84 (95% confidence interval 1.52-2.22). This finding does not necessarily indicate that atorvastatin increases the risk of deterioration in glycemic control because the comparison was made against pravastatin treatment.

The Collaborative Atorvastatin Diabetes Study investigated the protective effect of atorvastatin (10 mg/day) versus placebo specifically on cardiovascular disease in 2,838 patients with type 2 diabetes mellitus[14]. No difference was noted between the two regimens with respect to changes in HbA1c levels and the therapeutic modality for diabetes mellitus. The mean HbA1c levels at the baseline were 7.9% in the atorvastatin group and 7.8% in the placebo group. The corresponding values after 4 years of follow-up were 8.3% and 8.1%, respectively. At the baseline, insulin was used in 19.7% of patients in the atorvastatin group and 18.9% of patients in the placebo group. These proportions had not changed significantly at the end of the follow-up period (atorvastatin 20.5% and placebo 18.2%).

In summary, one study showed that pravastatin (40 mg/day) was protective against the development of diabetes mellitus. Two studies of atorvastatin (10 mg/day) and one study of simvastatin (40 mg/day) showed no measurable effect of these regimens on the risk of diabetes mellitus or the clinical course of diabetes mellitus. One study of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) suggested a deterioration of glucose metabolism associated with a high dose of atorvastatin. It should be noted that the onset or deterioration of diabetes mellitus was defined differently in the studies, however.

## Clinical Trials and Observational Studies in Japan

None of the reported clinical trials regarding statins and cardiovascular diseases has been extended to examine the effects of statins on the risk of diabetes mellitus or glucose metabolism[4, 15]. With hindsight, a possible adverse effect of atorvastatin on glucose metabolism was noted in a long-term one-arm trial of 287 patients with total cholesterol of ≥ 220 mg/dL. The primary purpose of this trial was to investigate the efficacy of atorvastatin 5-10 mg/day on serum lipids[16]. The majority (81%) of the patients received atorvastatin 10 mg/day throughout the study period. The prescribed dose was changed from 10 mg/day to 20 mg/day in 7% of the patients, from 10 mg/day to 5 mg/day in 5%, and from 5 mg/day to 10 mg/day in 4%. The episode of a pre-specified abnormal elevation of fasting blood glucose was fairly frequently observed during the one-year period, as shown in **Table 2**. Furthermore, the grade of abnormal elevation was more severe for blood glucose than for other laboratory measurements. Sixteen laboratory tests were evaluated in terms of severity. The majority (82%) of the episodes of abnormal change in laboratory tests other than glucose were classified as grade 1 (slight deterioration), but 15 of the 21 episodes of abnormal elevation of blood glucose were classified as grade 2 (moderate deterioration) or grade 3 (severe deterioration). The abnormal elevation of HbA1c was also commonly seen during the study period. It should be noted that the abnormal elevation of blood glucose or HbA1c was evaluated in terms of the number of episodes rather than cumulative incident cases.

We identified 11 published studies examining changes in fasting blood glucose and/or HbA1c after treatment with a specific statin in diabetes patients (**Table 3**). Of these, three were randomized trials[17-19], six were one-arm trials[20-25], and two were retrospective, observational studies[26, 27]. Except for three studies[22, 23, 26], these studies were very small in size with fewer than 100 patients, and a relatively short follow-up period. None of the seven trials found any measurable adverse effect of atorvastatin on glycemic con-

**Table 2.** Episodes of abnormal laboratory tests occurring in hypercholesterolemic patients treated with atorvastatin 5-20 mg/day for one year

| Abnormal laboratory test | No. of patients | No. of episodes |
|---|---|---|
| Elevation of gamma-glutamyltransferase | 287 | 50 (17.4%) |
| Elevation of alanine aminotrasferase | 287 | 34 (11.8%) |
| Elevation of aspartate aminotrasferase | 287 | 26 (9.1%) |
| Elevation of fasting blood glucose | 281 | 21 (7.5%) |
| Decreased testosterone | 274 | 20 (7.3%) |
| Elevation of creatinine phosphokinase | 287 | 19 (6.6%) |
| Elevation of choline esterase | 287 | 16 (5.6%) |
| Elevation of HbA1c | 282 | 15 (5.3%) |

Derived from reference (15)

**Table 3.** Clinical trials and observational studies concerning statins and glycemic control in patients with diabetes mellitus in Japan

| Authors (ref.) | Type of study | No. of patients | Statin | Dose (mg/day) | Period | Main findings |
|---|---|---|---|---|---|---|
| Tanaka, et al.[17] | RCT | 40 | Atorvastatin<br>Placebo | 10<br>– | 12 weeks | No change in HbA1c for each group. |
| Endo, et al.[18] | RCT | 47 | Atorvastatin<br>Pravastatin | 10<br>20 | 4 months | No change in HbA1c for each statin. |
| Kameda, et al.[19] | RCT | 14 | Atorvastatin<br>Bezafibrate | 10<br>400 | 9 months | No change in FBS/HbA1c for each drug. |
| Sato and Miyachi[20] | One-arm trial | 26 | Atorvastatin | 10-20 | 8 weeks on average | No change in HbA1c. |
| Hamano[21] | One-arm trial | 35 | Atorvastatin | 10 | 12 months | No change in FBS/HbA1c. |
| Sasamoto[22] | One-arm trial | 180 | Atorvastatin | 5-40 | 3-15 months | No change in FBS/HbA1c. |
| Suzuki[23] | One-arm trial | 160 | Atorvastatin | 10 | 3 months to 3 years | No change in HbA1c |
| Yamada, et al.[24] | One-arm trial | 27 | Pitavastatin | 2 | 8 weeks | HbA1c increased by 0.17% (95% CI 0.01, 0.33). |
| Yamada[25] | One-arm trial | 57 | Pitavastatin | 1-2 | 30 months on average | No change in FBS |
| Seino, et al.[26] | Observational study | 809 | Pravastatin<br>Simvastatin<br>Fluvastatin<br>Atorvastatin | 5-20<br>2.5-10<br>20-60<br>5-10 | 3.9 years<br>3.4<br>1.9<br>0.9 | No change in FBS/HbA1c for each statin. |
| Osaki, et al.[27] | Observational study | 67 | Atorvastatin<br>Pravastatin | 10<br>10 | 2-3 months | Deteriorated HbA1c (≥ 10% relatively) was more frequent for atorvastatin (7/25, 28%) than pravastatin (3/42, 7%). |

RCT: randomized controlled trial, FBS: fasting blood sugar.

trol[17-23]. Only one observational study reported that deterioration of HbA1c was statistically significantly more frequent for atorvastatin than pravastatin[27], whereas the other observational study found no measurable change in fasting blood glucose or HbA1c in relation to atorvastatin and other statins[26]. On the other hand, one of the two studies concerning pitavastatin showed a statistically significant increase in HbA1c after 8-week treatment[24]. Findings from case reports may often signal an alarming adverse effect of a newly introduced drug, but they may sometimes be an extreme of random variation. One study graphically presented HbA1c values of 26 subjects before and after atorvastatin treatment[20]. HbA1c increased markedly in a few individuals, and also decreased substantially in an almost equal number of subjects. Amelioration may not have been taken as seriously as deterioration in the routine clinical practice.

In summary, although the case reports suggested a potential adverse effect of atorvastatin in patients

with diabetes mellitus, none of the seven clinical trials provided supporting evidence. Only one of the two observational studies reported a more frequent deterioration of HbA1c in treatment with atorvastatin than with pravastatin. Observational findings in clinical practice require caution in their interpretation because they may have been ascribed to other concurrent factors associated with the deterioration of diabetes mellitus. Thus, evidence showing that atorvastatin at a dose commonly used in Japan deteriorates glycemic control in patients with diabetes mellitus is extremely limited.

## Mechanisms of the Effects of Statins on Glucose Metabolism

Evidence is very limited as regards the mechanisms by which statins exert any influence on glucose metabolism. Statins may improve insulin resistance and be protective against glucose intolerance through their anti-inflammatory effects[28, 29]. Inflammatory markers have been related to an increased risk of diabetes mellitus in adults[30, 31], and pro-inflammatory cytokines such as tumor necrosis factor (TNF)-$\alpha$ are implicated as being linked with insulin resistance through their influence on insulin receptor[32, 33]. On the other hand, statins can deteriorate glycemic control by decreasing various metabolites, such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and ubiquinone ($CoQ_{10}$), which are normally produced during the process of cholesterol synthesis from acetyl CoA via mevalonic acid. Isoprenoid is known to enhance glucose uptake by upregulating the membrane transporter protein glucose transporter 4 (Glut 4), which plays a role in glucose uptake in adipocytes[34]. Suppressed biosynthesis of ubiquinone ($CoQ_{10}$), an essential factor in the electron-transfer system in mitochondria, may result in delayed ATP production in pancreatic $\beta$ cells and thereby impair insulin release. It was recently shown that atorvastatin treatment resulted in a reduction of serum $CoQ_{10}$ levels, which was positively correlated with LDL cholesterol levels[35].

These mechanisms may differ by the property of statins. Water-soluble statins, such as pravastatin, are hepatocyte-specific and are not readily taken up by pancreatic cells and adipocytes. Lipid-soluble statins, such as simvastatin and atorvastatin, enter extrahepatic cells easily and may inhibit isoprenoid protein synthesis, consequently attenuating insulin action. Lovastatin, a lipid-soluble statin, was shown to down-regulate insulin-responsive Glut 4 and up-regulate Glut 1 in 3T3-L1 adipocytes leading to marked inhibition of insulin-stimulated glucose transport[34]. Another lipid-soluble statin, simvastatin, inhibited glucose-induced increase in intracellular $Ca^{2+}$ of pancreatic $\beta$ cells, leading to the inhibition of insulin secretion in a dose-dependent manner, while water-soluble pravastatin had absolutely no effect even at a high concentration of 100 $\mu$g/mL[36]. The inhibitory potency of HMG-CoA reductase and lipophilicity of statins may be related to different effects on glucose metabolism, although further studies are needed.

## Conclusion

A few clinical studies have suggested that atorvastatin, especially at a high dose, may deteriorate glucose metabolism while pravastatin might improve glucose metabolism; however, evidence is extremely limited, and further studies are needed to draw a conclusion on this issue. The mechanisms by which these statins affect glucose metabolism also need to be studied further. The effect of statins on glucose metabolism, if any, seems particularly important in Japan. Japanese are more prone to developing diabetes mellitus than Caucasians[37], and coronary risk is lower in Japan as compared with Western countries. A decreased risk of coronary artery disease conferred by statins well surpasses any adverse effect of intensive statin therapy in Western countries; however, it is uncertain whether such intensive statin therapy is also applicable in Japan.

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