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David C. Gaze*, Christian Prante, Jens Dreier, Cornelius Knabbe, Corinne Collet, Jean-Marie Launay, Janka Franekova, Antonin Jabor, Lieselotte Lennartz, Jessie Shih, Jose Manuel del Rey, Martina Zaninotto, Mario Plebani and Paul O. Collinson

Analytical evaluation of the automated galectin-3 assay on the Abbott ARCHITECT immunoassay instruments

Abstract

Background: Galectin-3 is secreted from macrophages and binds and activates fibroblasts forming collagen. Tissue fibrosis is central to the progression of chronic heart failure (CHF). We performed a European multicentered evaluation of the analytical performance of the two-step routine and Short Turn-Around-Time (*STAT*) galectin-3 immunoassay on the ARCHITECT $i1000_{SR}$, $i2000_{SR}$, and $i4000_{SR}$ (Abbott Laboratories).

Methods: We evaluated the assay precision and dilution linearity for both routine and *STAT* assays and compared serum and plasma, and fresh vs. frozen samples. The reference interval and biological variability were also assessed. Measurable samples were compared between ARCHITECT instruments and between the routine and *STAT* assays and also to a galectin-3 ELISA (BG Medicine).

Results: The total assay coefficient of variation (CV%) was 2.3%–6.2% and 1.7%–7.4% for the routine and *STAT* assays, respectively. Both assays demonstrated linearity up to 120 ng/mL. Galectin-3 concentrations were higher in plasma samples than in serum samples and correlated well between fresh and frozen samples (R=0.997), between the routine and STAT assays, between the ARCHITECT *i*1000 and *i*2000 instruments and with the galectin-3 ELISA. The reference interval on 627 apparently healthy individuals (53% male) yielded upper 95th and 97.5th percentiles of 25.2 and 28.4 ng/mL, respectively. Values were significantly lower in subjects younger than 50 years.

Conclusions: The galectin-3 routine and *STAT* assays on the Abbott ARCHITECT instruments demonstrated good analytical performance. Further clinical studies are required to demonstrate the diagnostic and prognostic potential of this novel marker in patients with CHF.

Keywords: analytical performance; ARCHITECT; chronic heart failure; galectin-3.

***Corresponding author: David C. Gaze,** Chemical Pathology, Clinical Blood Sciences, St. George's Healthcare NHS Trust, Blackshaw Road, London SW17 0QT, UK, Phone: +44 208 725 5878, Fax: +44 208 725 5868, E-mail: david.gaze@stgeorges.nhs.uk
Christian Prante, Jens Dreier and Cornelius Knabbe: Heart and Diabetes Center North Rhine Westphalia, Institute for Laboratory and Transfusion Medicine, Bad Oeynhausen, Germany
Corinne Collet and Jean-Marie Launay: Laboratory of Clinical Biochemistry, Lariboisière Hospital, Paris, France
Janka Franekova and Antonin Jabor: Department of Laboratory Methods, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
Lieselotte Lennartz: Abbott Laboratories, Wiesbaden, Germany
Jessie Shih: Abbott Laboratories, Abbott Park, IL, USA
Jose Manuel del Rey: Core Laboratory, Clinical Chemistry, Ramon y Cajal Hospital, Madrid, Spain
Martina Zaninotto and Mario Plebani: Department of Laboratory Medicine, University Hospital of Padova, Padua, Italy
Paul O. Collinson: Chemical Pathology, Clinical Blood Sciences, St. George's Healthcare NHS Trust, London, UK

Introduction

Heart failure is common in Europe, affecting approximately 1%–2% of the adult population [1]. The incidence and prevalence increases with age with the average age of diagnosis being 76 years [2]. The risk of chronic heart failure (CHF) is greater in men than women, but there are more women with CHF than men due to population demographics [1]. Prognosis is poor; 40% of patients die within 1 year of diagnosis, and survival is lower than 10% per year thereafter [3]. Echocardiography and biochemical assays for natriuretic peptides (NTproBNP or BNP) are routinely used for diagnosis and management of cardiac heart failure patients [1].

Galectin-3 (~30 kDa, LGALS3, Chr 14,q21–q22) is a β-galactoside-binding lectin secreted from macrophages [4]. Galectin-3 is involved in inflammation and in the pathogenesis of tumor growth and autoimmune conditions [5]. Galectin-3 binds to and activates fibroblasts

forming collagen and results in fibrosis (scaring) [6]. Galectin-3 has been associated with tissue repair, cardiac inflammation, and cardiac remodeling [6–11]. Tissue fibrosis is the final common pathway central to the progression of CHF. Diffuse cardiac fibrosis impairs ventricular function and contributes to both systolic and diastolic dysfunction. Galectin-3 therefore is a potential diagnostic and prognostic marker of CHF as well as a surrogate marker to assess therapeutic intervention aimed at reducing the progression of CHF [12–15].

The enzyme-linked immunosorbent assay (ELISA) commercially available for the measurement of galectin-3 presents satisfactory quality specifications but requires some manual steps [16]. High-throughput assays allowing automation and a shorter turn around time on immunoassay analyzers will be required for the measurement of galectin-3 in routine clinical use. We performed a multicentered evaluation of the analytical performance of the two-step routine and Short Turn-Around-Time (*STAT*) galectin-3 immunoassays on the ARCHITECT $i1000_{SR}$, $i2000_{SR}$, and $i4000_{SR}$ (Abbott Laboratories, Wiesbaden, Germany) at six European sites.

Materials and methods

Sites, instruments, and reagents

The ARCHITECT Galectin-3 assay is a chemiluminescent microparticle immunoassay for the quantitative determination of galectin-3 in human serum or EDTA plasma performed on the ARCHITECT *i* systems. The assay is a two-step protocol. In step 1, 25 µL of sample and M3/M38 anti-galectin-3-coated paramagnetic microparticles are incubated. Galectin-3 molecules present in the sample bind the M3/M38 antibody. Following a wash step, the second step incorporates the addition of a B7/B5 anti-galectin-3 acridinium-labeled conjugate, creating an antibody-antigen sandwich. After a further washing cycle, a pre-trigger and trigger solutions are added to the reaction vessel, creating a chemiluminescent reaction. The light emission is measured as relative light units by a photomultiplier and is directly proportional to the amount of galectin-3 in the sample. The routine assay takes 29 min. The short *STAT* assay also uses 25 µL of sample and can be processed in 18 min.

The routine assay was assessed in the UK on an $i2000_{SR}$ (site 1) and in Germany on an $i4000_{SR}$ (site 2). The *STAT* version of the assay was also investigated in the UK ($i2000_{SR}$) as well as in France (site 3, on two $i2000_{SR}$ instruments), the Czech Republic (site 4), Italy (site 6) on the $i2000_{SR}$ and in Spain (site 5) on the $i1000_{SR}$.

An ELISA plate assay (BG Medicine, Waltham, MA, USA) was available for methodological comparison. The limit of blank (LoB) was 0.86 ng/mL, the limit of detection (LoD) was 1.13 ng/mL, and the limit of quantification (LoQ) was 1.32 ng/mL. The coefficient of variation (%CV) was 4.2% to 12.0% at 6.1 to 72.2 ng/mL. The dynamic measuring range of the ELISA assay was 1.32 to 96.6 ng/mL.

Assay precision and limits of blank, detection, and quantification

The assay precision was determined at each site following the Clinical and Laboratory Standards Institute (CLSI) EP5-A2, based on 20 replicates of the low-, medium-, and high-concentration assay quality controls (QC). QC materials were assayed in duplicate in two runs, separated by a minimum of 2 h and run over 5 days.

The LoB, LoD, and LoQ were verified for both the ARCHITECT Galectin-3 routine and *STAT* assays and performed according to CLSI guideline EP17-A on each analyzer. For LoB, 20 replicates of a blank material (Calibrator A, 0.0 ng/mL) were tested. For LoD verification, 20 replicates of a sample with a concentration close to the manufacturers claimed LoD were used. LoQ was verified by testing a minimum of 30 replicates of a sample with a concentration near the claimed LoQ. The LoB, LoD, and LoQ ranged from 0.2 to 0.3, from 0.6 to 0.7, and from 5.0 to <6.0 ng/mL, respectively, for the routine assay and from 0.0 to 1.2, from 0.5 to 1.7, and from 2.1 to 4.0 ng/mL for the *STAT* assay, respectively (Table 1).

Table 1 Total assay precision (%CV) using QC material and LoB, LoD, and LoQ.

	Site 1		Site 2	Site 3		Site 4	Site 5	Site 6
	UK	UK	Germany	France 1	France 2	Czech Republic	Spain	Italy
Instrument	$i\ 2000_{SR}$	$i\ 2000_{SR}$	$i\ 4000_{SR}$	$i\ 2000_{SR}$	$i\ 2000_{SR}$	$i\ 2000_{SR}$	$i\ 1000_{SR}$	$i\ 2000_{SR}$
Assay format	Routine	*STAT*	Routine	*STAT*	*STAT*	*STAT*	*STAT*	STAT
Low QC (9.1 ng/mL), mean±SD	9.9±0.6	9.8±0.6	9.3±0.6	9.9±0.5	9.3±0.7	8.8±0.5	9.0±0.4	9.3±0.4
Low QC, %CV	6.2	5.9	6.0	4.5	7.4	5.3	4.6	3.8
Medium (20.5 ng/mL), mean±SD	20.8±0.6	20.8±0.4	20.2±0.9	21.2±0.9	19.9±0.7	19.5±0.7	20.1±0.5	19.6±0.4
Medium QC, %CV	2.8	1.9	4.3	4.0	3.6	3.3	2.4	2.0
High QC (74.1 ng/mL), mean±SD	74.5±1.8	74.5±1.7	75.2±2.2	77.1±2.7	76.2±2.5	71.6±2.1	73.6±1.8	73.7±1.3
High QC, %CV	2.3	2.0	2.9	3.5	3.3	3.0	2.5	1.7
LoB, ng/mL	0.3	0.0	0.2	0.4	[a]	N/A	0.4	1.2
LoD, ng/mL	0.7	0.5	0.6	0.6	[a]	0.7	0.7	1.7
LoQ, ng/mL	5.0	4.0	<6.0	4.0	[a]	2.1	4.0	<4.0

[a]LoB, LoD, and LoQ were determined at site 3 on one instrument only.

Dilution linearity

Linearity was assessed by making five dilutions of a high-patient sample containing an analyte concentration near the upper end of the analytical measurement range (AMR), with a low patient sample. Each dilution was tested in duplicate. Both the routine and *STAT* assays demonstrated dilution linearity up to 120 ng/mL (regression equation -2.454+1.036×).

Sample matrix comparison

Matched serum and EDTA plasma samples were drawn from 54 subjects and assayed fresh on the Galectin-3 *STAT* assay.

Fresh samples compared with frozen samples

The effects of sample freezing were assessed. EDTA plasma samples (n=36) were collected in the morning and stored at 2°C–8°C. Samples were divided into two aliquots: one aliquot was tested on the same day for both methods, and the other aliquot was frozen at -30°C for 2 days, thawed, mixed, and reassayed on both methods.

Methodological comparison

Samples with concentrations of galectin-3 across the measuring range were compared in three experiments. First, comparisons were made between the routine and *STAT* assay. Second, comparisons were made between the $i1000_{SR}$ and $i2000_{SR}$ instruments. Third, samples were compared between the ARCHITECT galectin-3 and the BG Medicine galectin-3 ELISA.

Reference interval

The reference interval was investigated using 627 samples from apparently healthy individuals with no evidence of cardiac disease. Site 1 (n=120) used fresh serum from apparently cardiac healthy individuals with negative serum cTnI as defined by the Siemens Centaur TnI-Ultra assay and normal NTproBNP concentrations determined on the Siemens IMMULITE 2000 XPi. Site 2 (n=130) used frozen plasma and site 6 (n=136) used fresh serum samples from unscreened apparently healthy volunteers. Site 3 (n=119) used frozen serum samples from volunteers self-reporting the absence of a history of diabetes, hypertension, cardiovascular disease, or cancer. Site 5 (n=122) used fresh plasma samples from healthy individuals attending a routine medical checkup appointment. At all sites, the subject's age and gender were recorded.

Biological variability

The biological variability of galectin-3 was determined in healthy individuals recruited at sites 2 (n=12) and 3 (n=18). All subjects were bled twice within the same day, in the morning and the afternoon. In addition, subjects recruited at site 2 were also bled for five consecutive days. Samples were assayed fresh for galectin-3.

Samples source, data handling, and statistics

Ethics approval was received for specimens collected for the reference interval and biological variation studies, and waiver was received for the use of surplus specimens. Data from each site were recorded in Microsoft Excel spreadsheets (Microsoft Corporation, Redmond, WA, USA). Assay precision, linearity, reference intervals, Passing-Bablok, and linear regression analyses were generated using Analyse-it (Analyse-it Software, Leeds, UK; http://analyse-it.com). The short-term (within day) and long-term (between 5 days) biological variability were calculated according to the methods of Fraser and Harris [17].

Results

Imprecision based on manufacturer's QC material was favorable and demonstrated total assay %CV of <7% for the routine assay and <8% for the *STAT* assay, irrespective of platform. The imprecision for each site is summarized in Table 1. The results were similar between sites. The least precise QC occurred in the *STAT* assay using the low QC (9.3 ng/mL, %CV=7.4%), whereas the most precise occurred in the high QC (73.7 ng/mL, %CV=1.7%) for the *STAT* assay.

Verification of the manufacturer's claimed LoB, LoD, and LoQ were determined by CLSI guidelines. The LoB, LoD, and LoQ ranged from 0.2 to 0.3, from 0.6 to 0.7, and from 5.0 to <6.0 ng/mL, respectively, for the routine assay and from 0.0 to 1.2, from 0.5 to 1.7, and from 2.1 to 4.0 ng/mL for the *STAT* assay, respectively (Table 1). Both the routine and *STAT* assays demonstrated dilutional linearity up to 120 ng/mL (regression equation -2.454+1.036×) (Supplemental Data, Table 1 and Figure 1, which accompany the article at http://www.degruyter.com/view/j/cclm.2014.52.issue-6/issue-files/cclm.2014.52.issue-6.xml).

Observable differences between serum and plasma were assessed. Matched serum and plasma (n=54) samples taken at the same draw were measured for galectin-3. There was no significant difference between serum and plasma in 10 samples measured at site 5; however, using a larger population of 44 samples at site 6, galectin-3 concentration were significantly higher in plasma compared with serum ($p \leq 0.001$). When combining the data, the mean plasma galectin-3 concentration was 39.5 ng/mL but was 36.8 ng/mL in serum samples (Passing-Bablok regression, -1.60+0.99×, Figure 1A; bias of -10.2%; 95% CI, -36.8% to 16.3%, Figure 1B).

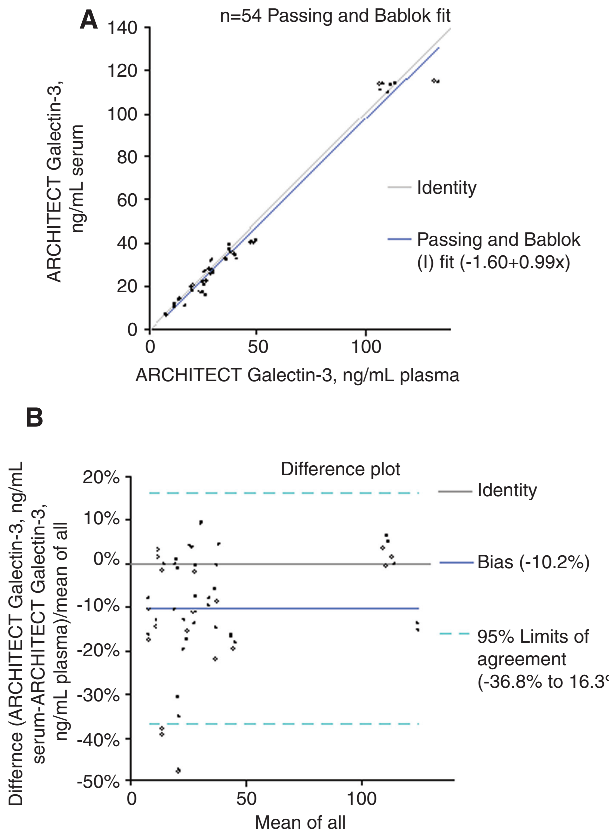

Figure 1 Sample matrix comparison.
(A) Passing-Bablok scatter plot and (B) Bland-Altman difference plots of serum and plasma galectin-3 concentrations.

Galectin-3 concentrations were similar (r=0.997, Passing-Bablok regression, 0.86+1.07×, bias 10.1%; 95% CI, -6.0% to 26.2%) between fresh samples (n=36, median galectin-3, 17.7 ng/mL) and frozen samples thawed once and reassayed (median galectin-3, 18.6 ng/mL). This was similar for the BG Medicine ELISA assay (r=0.999, Passing-Bablok regression, 0.38+1.11×, bias 12.8% (95% CI, -3.5% to 29.0%) (Supplemental Data, Table 2).

There was good correlation between the routine and *STAT* galectin-3 assay formats (n=105, Passing-Bablok regression, -0.52+1.04×, bias 2.0%; 95% CI, -11.0% to 15.1%, Figure 2A). Excellent correlation was observed between the ARCHITECT *i*1000 and *i*2000 instruments (n=30, Passing-Bablok regression, 0.33+0.99×, bias -0.8%; 95% CI, -9.4% to 7.9%, Figure 2B). Consolidating the results from all sites in the largest comparison (n=807), there was good agreement between the ARCHITECT assay and the BG Medicine galectin-3 ELISA (Passing-Bablok regression, -0.07+1.04×, bias 6.7%; 95% CI, -32.3% to 45.6%, Figure 2C).

A population of 627 apparently healthy individuals comprising 335 males and 292 females with no evidence of cardiac disease was used to determine the galectin-3 reference intervals. The combined data are summarized in Table 2 and presented as the upper 75th, 95th, and 97.5th percentiles for the entire cohort and according to gender and age. The frequency distribution of galectin-3 concentrations is shown in Figure 3A. The greatest frequency of concentrations occurred at approximately 12.5 ng/mL. A weak trend between increasing age and galectin-3 concentration was observed (Figure 3B). Similar trends were observed in both males (Supplemental Data, Figure 2A) and females (Supplemental Data, Figure 2B).

The biological variability of galectin-3 was assessed at two sites. The within subject (CVi) and between subject (CVg) biological variability were 10.3% and 22.4%, respectively, with a reference change value (RCV) of 30.7 for within-day variation and 13.1% and 26.8%, respectively, with an RCV of 38.0 for between 5-day variability. Combining all available data from the two sites the total biological variability of galectin-3 was 14.4% CVi and 23.3% CVg with an RCV of 43.5 (Table 3). There was a demonstrable difference in the variability of galectin-3 in females compared with males (Supplemental Data, Figure 3).

Discussion

The performance characteristics of the ARCHITECT Galectin-3 automated immunoassay demonstrates that it is suitable both as a routine and short turn-around-time assay for the determination of galectin-3 using the validated sample matrix, either serum or EDTA plasma. The assay demonstrated better precision than that reported previously for the BG Medicine ELISA assay [16]. These data presented in the present multicenter European study are similar to precision data obtained in a two-site American study [18] that also obtained total %CV <6% across two reagent lots, when employing both the $i1000_{SR}$ and $i2000_{SR}$ instruments. The assay has a wide dynamic linear range suitable for the clinical utility in CHF patients. The assay is robustly stable with no significant difference between fresh and frozen samples. Similar findings of galectin-3 stability have been observed over the course of 2 weeks when samples are stored either at room temperature or refrigerated or subjected to six freeze-thaw cycles [16]. In the present study, galectin-3 was higher in plasma than in serum ($p \leq 0.001$); however, there is equal variance for the values in both matrices. This is contrary to the findings of La'ulu and colleagues [18] who demonstrated similar values between serum and EDTA plasma; however, they only compared 11 paired samples, whereas the present

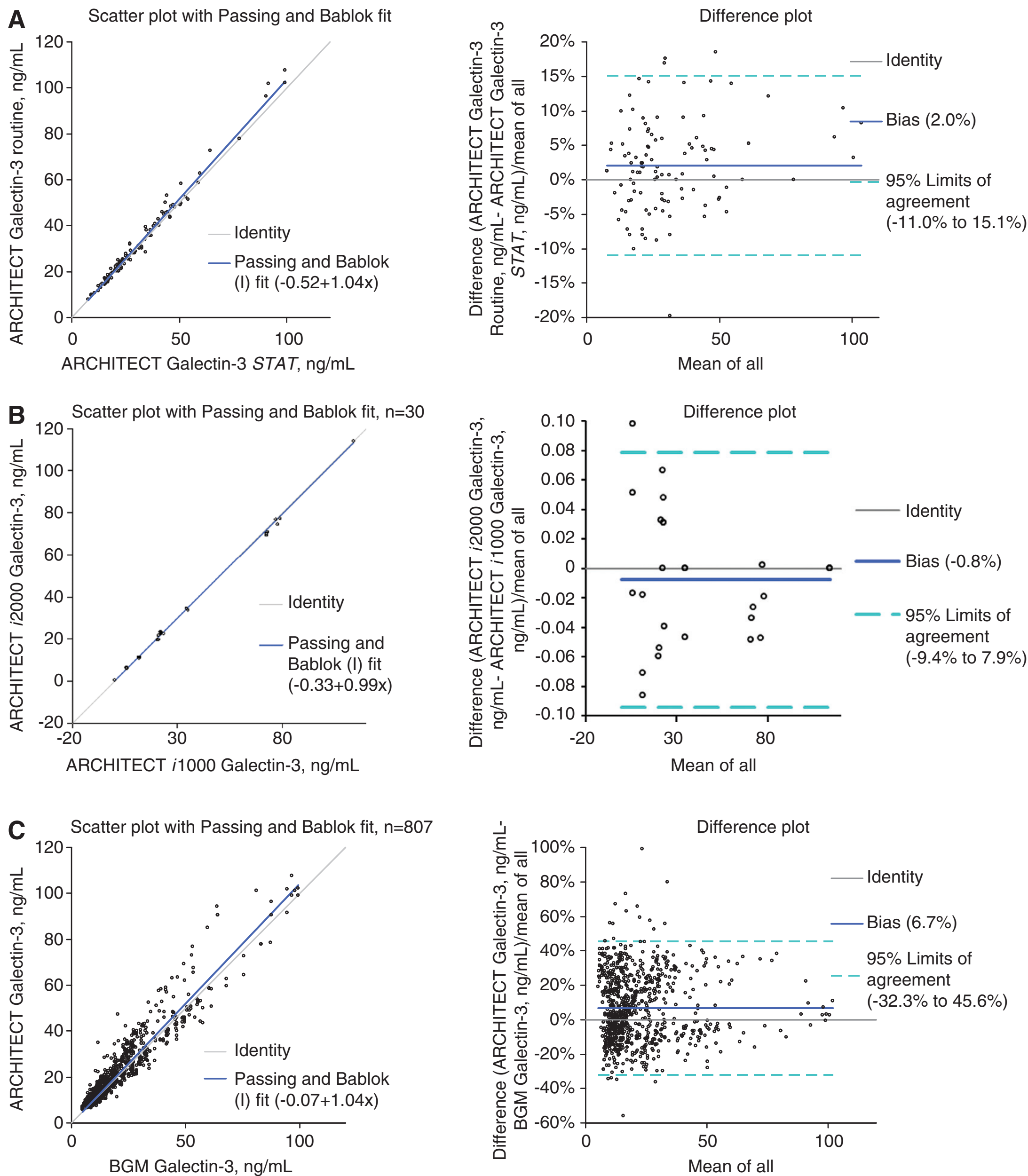

Figure 2 Method comparison studies.
(A) Comparison between galectin-3 routine and *STAT* assay. (B) Comparison between galectin-3 determined on the $i1000_{SR}$ and $i2000_{SR}$ ARCHITECT instruments. (C) Compared between the ARCHITECT Galectin-3 assay and the galectin-3 ELISA.

Table 2 Galectin-3 reference interval: log-transformed upper 75th, 95th, and 97.5th percentile in all healthy individuals and stratified by gender and age, 50 years or younger or older than 50 years.

	n	Mean, ng/mL	Median, ng/mL	75th Percentile, ng/mL	95th Percentile, ng/mL	97.5th Percentile, ng/mL
All	627	14.6	13.3	17.5	25.2	28.4
Males	335	14.8	13.7	17.8	25.9	33.3
Females	292	14.3	13.1	17.1	24.4	27.3
<50 years	457	13.7	12.5	16.3	22.9	25.5
≥50 years	170	16.8	15.0	20.5	30.8	35.1

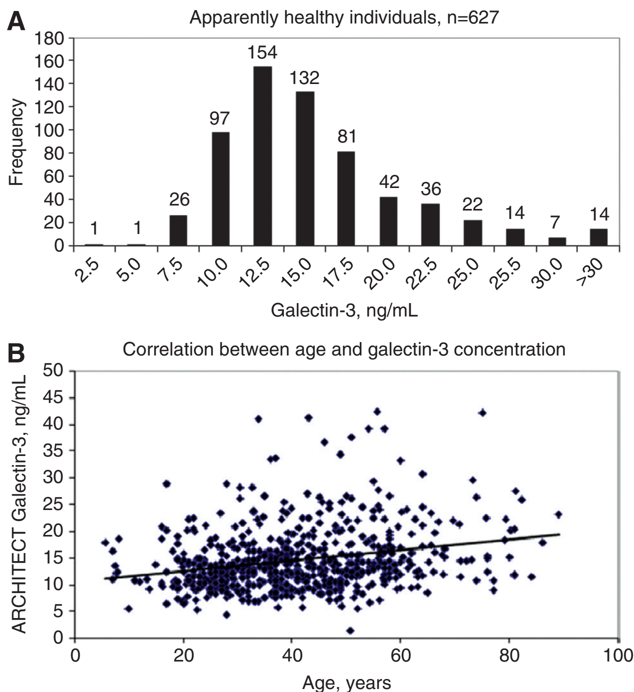

Figure 3 Galectin-3 reference population.
(A) Frequency distribution of galectin-3 concentrations in apparently healthy individuals. (B) Correlation of galectin-3 concentrations according to age in apparently healthy individuals.

study included 54. Additionally, Christenson et al. [16] found similar values in 50 matched serum and EDTA plasma samples when using the BG Medicine ELISA assay.

A number of method comparisons were performed in the present study. There was good overall agreement between the two assay formats, between different instruments of the ARCHITECT family, and between the automated assay and the comparator BG Medicine ELISA assay. Comparing 807 samples between the ARCHITECT and the comparator method, there was very little difference with a small positive bias of 6.7% toward the ARCHITECT method. These data suggest that clinical studies performed on the ELISA assay can be extrapolated to the ARCHITECT, but the automated assay should be robustly investigated independently for its clinical utility.

The distribution of galectin-3 concentrations in 1092 apparently healthy individuals has been studied previously using the BG Medicine ELISA assay. The 95th and 97.5th percentiles were found to be 20.3 and 22.1 ng/mL, respectively. The upper reference limits derived in the present study based on 627 individuals considered to be healthy were slightly higher at 25.2 and 28.4 ng/mL, respectively, for the automated ARCHITECT assay. In the comparative study from the USA, these values were much lower at <20 ng/mL for both the 95th and 97.5th percentile. It is probable that the smaller data set (n=364) and a wider age distribution (range, 19–79 years) in the US study is responsible for the disparity. De Boer and colleagues have previously investigated 7968 general population subjects as part of the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) cohort and found a strong association between galectin-3 and increasing age and gender [19]. Concentrations of galectin-3, determined using the BG Medicine ELISA, were greater in women than in men across the age range, 30–75 years. A similar but less striking trend was observed in the current data set (Table 2), which is probably attributable to the small gender-specific populations studied. Larger data sets should be investigated using the automated ARCHITECT assay. A significant difference between male and female galectin-3 concentrations was observed at sites 2 and 3, whereas all other sites did not demonstrate a difference between the gender groups. No significant differences were demonstrated in the US study [18]. Instrumentation and assay differences can be ruled out as an explanation as the sites differed by using *i*4000$_{SR}$ routine and *i*2000$_{SR}$ *STAT* galectin-3 assays, respectively. The large general population studied by de Boer showed divergence of galectin-3 trend lines between males and females older than 50 years, yet values were similar between the gender groups younger than 50 years old. It is possible that this phenomenon is responsible for lack of difference observed between the gender groups at most of the sites in this study. A further limitation to our reference interval study was the lack of ethnographic data, history of cardiovascular disease

Table 3 Biological variability of galectin-3.

	Short-term (within day)	Long-term (5 days)	Combined overall
Mean galectin-3, ng/mL	12.9	10.9	11.4
Analytical variation, CVa%	4.1	4.1	6.2
Within-subject biological variation, % CVi	10.3	13.1	14.4
Between-subject biological variation, % CVg	22.4	26.8	23.3
Index of individuality, II	0.50	0.50	0.67
RCV	30.7	38.0	43.5

including diabetes mellitus, or the use of cardiovascular medication. Furthermore, we did not report renal function in the apparently healthy population. It has been established recently that elevated plasma galectin-3 concentrations are associated with decreased eGFR. O'Seaghdha and colleagues [20] measured plasma galectin-3 in 2450 Framingham offspring participants. Elevated plasma galectin-3 was associated with a rapid decline in eGFR (odds ratio 1.49; 95% CI, 1.28 to 1.73) and to a higher risk of chronic kidney disease (odds ratio 1.47; 95% CI, 1.27 to 1.71). Further studies are required to assess differences in galectin-3 within the healthy population based on ethnicity, prior history of cardiovascular disease, and associated risk factors including renal function status.

The use of age- and gender-specific reference limits has been proposed for other cardiac biomarkers such as NTproBNP, BNP, and cardiac troponin rather than a single value, and it is likely that the same should be applied to galectin-3.

We report here to the best of our knowledge for the first time, the biological variability of galectin-3 in the general population as determined by the ARCHITECT automated immunoassay. The biological variation of galectin-3 based on the BG Medicine ELISA assay has been reported in a small study (n=17) previously [21]. The RCVs reported in the present study are lower than the hourly RCV (39%) or the long-term RVC (8 weeks) (61%), as previously reported. In addition, the biological variation of galectin-3 is lower than the long-term biological variation of BNP (RCV 140%), which suggests galectin-3 may be a better marker to guide therapy than BNP. Galectin-3 is a specific biomarker of fibrosis, a known indicator of CHF progression. Although the natriuretic peptides can also detect the consequences of fibrosis, they are influenced by fluid and volume overload [22] and thus may be less specific.

In summary, this multicentered European study has evaluated the analytical performance of the ARCHITECT Galectin-3 immunoassay. The assay demonstrated good imprecision and linearity and acceptable comparison to an ELISA method. An automated immunoassay is less labor-intensive and facilitates faster turn-around times than a manual ELISA, thus facilitating the execution of more clinical studies to further establish the relevance and application of galectin-3 testing in clinical practice.

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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